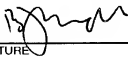


FORM PTO-1586 (REV 11-2000)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S CHECK NUMBER <b>1721-43</b>
<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</b>		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) <b>10/030740</b> <small>Unknown</small>
INTERNATIONAL APPLICATION NO. <b>PCT/EP00/06943</b>	INTERNATIONAL FILING DATE <b>5 July 2000</b>	PRIORITY DATE CLAIMED <b>13 July 1999</b>
TITLE OF INVENTION <b>NOVEL NEISSERIA MENINGITIDIS COMPOUNDS AND ANTI-INFECTION APPLICATIONS THEREOF</b>		
APPLICANT(S) FOR DO/EO/US <b>NASSIF et al</b>		
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:		
1. <input checked="" type="checkbox"/> This is a <b>FIRST</b> submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a <b>SECOND</b> or <b>SUBSEQUENT</b> submission of items concerning a filing under 35 U.S.C. 371. 3. <input checked="" type="checkbox"/> This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below. 4. <input checked="" type="checkbox"/> The U.S. has been elected by the expiration of 19 months from the priority date (Article 31). 5. A copy of the International Application as filed (35 U.S.C. 371(c)(2)). a. <input type="checkbox"/> is attached hereto (required only if not communicated by the International Bureau). b. <input checked="" type="checkbox"/> has been communicated by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US). 6. <input type="checkbox"/> An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)). a. <input type="checkbox"/> is attached hereto. b. <input type="checkbox"/> has been previously submitted under 35 U.S.C. 154(d)(4). 7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)). a. <input type="checkbox"/> are attached hereto (required only if not communicated by the International Bureau). b. <input type="checkbox"/> have been communicated by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has <b>NOT</b> expired. d. <input type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input type="checkbox"/> A English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).  <b>Items 11 to 20 below concern document(s) or information included:</b> 11. <input type="checkbox"/> An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included. 13. <input checked="" type="checkbox"/> A <b>FIRST</b> preliminary amendment. 14. <input type="checkbox"/> A <b>SECOND</b> or <b>SUBSEQUENT</b> preliminary amendment. 15. <input type="checkbox"/> A substitute specification. 16. <input type="checkbox"/> A change of power of attorney and/or address letter. 17. <input checked="" type="checkbox"/> A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825. and hard copy. 18. <input type="checkbox"/> A second copy of the published international application under 35 U.S.C. 154(d)(4). 19. <input type="checkbox"/> A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4). 20. <input checked="" type="checkbox"/> Other items or information. PTO-1449 and copy of International Search Report; Statement re: Sequence Listing		

11 JAN 2002

U.S. APPLICATION NO. (if known) <b>107030740</b>		INTERNATIONAL APPLICATION NO. <b>PCT/EP00/06943</b>		ATTORNEY'S DOCKET NUMBER <b>1721-43</b>	
21. <input checked="" type="checkbox"/> The following fees are submitted:				<b>CALCULATIONS</b> PTO USE ONLY	
<b>BASIC NATIONAL FEE (37 C.F.R. 1.492(a)(1)-(5):</b> -- Neither international preliminary examination fee (37 C.F.R. 1.482) nor international search fee (37 C.F.R. 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO.....\$1040.00 -- International preliminary examination fee (37 C.F.R. 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO.....\$890.00 -- International preliminary examination fee (37 C.F.R. 1.482) not paid to USPTO but international search fee (37 C.F.R. 1.445(a)(2)) paid to USPTO.....\$740.00 -- International preliminary examination fee (37 C.F.R. 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4).....\$710.00 -- International preliminary examination fee (37 C.F.R. 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4).....\$100.00  <b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b>				\$	890.00
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 C.F.R. 1.492(e)).				\$	130.00
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	24	-20 =	4	X	\$18.00
Independent Claims	8	-3 =	5	X	\$84.00
MULTIPLE DEPENDENT CLAIMS(S) (if applicable)					\$280.00
<b>TOTAL OF ABOVE CALCULATIONS =</b>				\$	1512.00
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.					0.00
<b>SUBTOTAL =</b>				\$	1512.00
Processing fee of \$130.00, for furnishing the English Translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 C.F.R. 1.492(f)).				+	0.00
<b>TOTAL NATIONAL FEE =</b>				\$	1512.00
Fee for recording the enclosed assignment (37 C.F.R. 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. 3.28, 3.31). \$40.00 per property				+	0.00
Fee for Petition to Revive Unintentionally Abandoned Application (\$1280.00 - Small Entity = \$640.00)				\$	0.00
<b>TOTAL FEES ENCLOSED =</b>				\$	1512.00
				Amount to be:	
				refunded	\$
				Charged	\$
a. <input checked="" type="checkbox"/> A check in the amount of \$1512.00 to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. 14-1140 in the amount of \$_____ to cover the above fees. A duplicate copy of this form is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-1140. A duplicate copy of this form is enclosed. d. <input checked="" type="checkbox"/> The entire content of the foreign application(s), referred to in this application is/are hereby incorporated by reference in this application.					
<b>NOTE: Where an appropriate time limit under 37 C.F.R. 1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</b>					
<b>SEND ALL CORRESPONDENCE TO:</b>  NIXON & VANDERHYE P.C. 1100 North Glebe Road, 8 <sup>th</sup> Floor Arlington, Virginia 22201-4714 Telephone: (703) 816-4000					
				SIGNATURE 	
				<b>B. J. Sadoff</b> NAME	
36,663				January 11, 2002	
REGISTRATION NUMBER				Date	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#4/a

In re Patent Application of

NASSIF et al

Atty. Ref.: 1721-43

Serial No. Unknown

Group:

National Phase of: PCT/EP00/06943

International Filing Date: 5 July 2000

Filed: Herewith

Examiner:

For: NOVEL NEISSERIA MENINGITIDIS COMPOUNDS AND  
ANTI-INFLECTION APPLICATIONS THEREOF

\* \* \* \* \*

January 11, 2002

Assistant Commissioner for Patents  
Washington, DC 20231

Sir:

**PRELIMINARY AMENDMENT**

Prior to calculation of the filing fee, please amend the application as follows:

**IN THE SPECIFICATION**

Page 1, after the title insert the following:

-- This application is the US national phase of international application PCT/EP00/06943  
filed July 5, 2000 which designated the U.S. --.

**IN THE CLAIMS**

Please substitute the following amended claims for corresponding claims previously  
presented. A copy of the amended claims showing current revisions is attached.

5. (Amended) An immunogenic fragment of the polypeptide as claimed in claim 1 in  
which the immunogenic activity of said immunogenic fragment is substantially the same as the  
polypeptide of SEQ ID NO:2, SEQ ID NO : 4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO : 10,  
SEQ ID NO : 12, SEQ ID NO : 14, SEQ ID NO : 16, SEQ ID NO : 18, SEQ ID NO : 20, SEQ  
ID NO : 22, SEQ ID NO : 24, SEQ ID NO : 26, SEQ ID NO : 28, SEQ ID NO : 30, SEQ ID NO  
: 32, SEQ ID NO : 34, SEQ ID NO : 36, SEQ ID NO : 38, SEQ ID NO : 40, SEQ ID NO : 42,

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SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID NO : 48, SEQ ID NO : 50, SEQ ID NO : 52, SEQ ID NO : 54, SEQ ID NO : 56, SEQ ID NO : 58, SEQ ID NO : 60, SEQ ID NO : 62, SEQ ID NO : 64, SEQ ID NO : 66, SEQ ID NO : 68, SEQ ID NO : 70, SEQ ID NO : 72, SEQ ID NO : 74, SEQ ID NO : 76, SEQ ID NO : 78, SEQ ID NO : 80, SEQ ID NO : 82, SEQ ID NO : 84, SEQ ID NO : 86, SEQ ID NO : 88, SEQ ID NO : 90.

9. (Amended) The isolated polynucleotide as claimed in claim 6 in which the identity is at least 95% to SEQ ID NO : 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89.

13. (Amended) An expression vector or a recombinant live microorganism comprising an isolated polynucleotide according to claim 6.

16. (Amended) A process for expressing a polynucleotide of claim 6 comprising transforming a host cell with the expression vector comprising at least one of said polynucleotides and culturing said host cell under conditions sufficient for expression of any one of said polynucleotides.

17. (Amended) A vaccine composition comprising an effective amount of the polypeptide of claim 1 and a pharmaceutically acceptable carrier.



18. (Amended) A vaccine composition comprising an effective amount of the polynucleotide of claim 6 and a pharmaceutically effective carrier.

19. (Amended) The vaccine composition according to claim 17 wherein said composition comprises at least one other *Neisseria meningitidis* antigen.

20. (Amended) An antibody immunospecific for the polypeptide or immunological fragment as claimed in claim 1.

21. (Amended) A method of diagnosing a *Neisseria* infection, comprising identifying a polypeptide as claimed in claim 1, or an antibody that is immunospecific for said polypeptide, present within a biological sample from an animal suspected of having such an infection.

22. (Amended) Use of a composition comprising an immunologically effective amount of a polypeptide as claimed in claim 1 in the preparation of a medicament for use in generating an immune response in an animal.

23. (Amended) Use of a composition comprising an immunologically effective amount of a polynucleotide as claimed in claim 6 in the preparation of a medicament for use in generating an immune response in an animal.

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24. (Amended) A therapeutic composition useful in treating humans with Neisseria meningitidis disease comprising at least one antibody directed against the polypeptide of claim 1 and a suitable pharmaceutical carrier.

**REMARKS**

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

The above amendments are made to place the claims in a more traditional format.

A paper and computer-readable form of the Sequence Listing are attached. The attached paper and computer-readable copies of the Sequence Listing are the same. No new matter has been added. A separate Statement to this effect is attached. A separate amendment to the specification to include the Sequence Listing is not believed to be required however the Office is requested to advise the undersigned if otherwise.

Return of an initialed copy of the attached PTO-1449 Form, pursuant to MPEP §609, is requested.

An early and favorable Action on the merits is requested.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

By: 

**B. J. Sadoff**

Reg. No. 36,663

**BJS:lmy**

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

5. (Amended) An immunogenic fragment of the polypeptide as claimed in [any one of claims 1 to 4] claim 1 in which the immunogenic activity of said immunogenic fragment is substantially the same as the polypeptide of SEQ ID NO:2, SEQ ID NO : 4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO : 10, SEQ ID NO : 12, SEQ ID NO : 14, SEQ ID NO : 16, SEQ ID NO : 18, SEQ ID NO : 20, SEQ ID NO : 22, SEQ ID NO : 24, SEQ ID NO : 26, SEQ ID NO : 28, SEQ ID NO : 30, SEQ ID NO : 32, SEQ ID NO : 34, SEQ ID NO : 36, SEQ ID NO : 38, SEQ ID NO : 40, SEQ ID NO : 42, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID NO : 48, SEQ ID NO : 50, SEQ ID NO : 52, SEQ ID NO : 54, SEQ ID NO : 56, SEQ ID NO : 58, SEQ ID NO : 60, SEQ ID NO : 62, SEQ ID NO : 64, SEQ ID NO : 66, SEQ ID NO : 68, SEQ ID NO : 70, SEQ ID NO : 72, SEQ ID NO : 74, SEQ ID NO : 76, SEQ ID NO : 78, SEQ ID NO : 80, SEQ ID NO : 82, SEQ ID NO : 84, SEQ ID NO : 86, SEQ ID NO : 88, SEQ ID NO : 90.

9. (Amended) The isolated polynucleotide as claimed in [any one of claims 6 to 8] claim 6 in which the identity is at least 95% to SEQ ID NO : 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89.

13. (Amended) An expression vector or a recombinant live microorganism comprising an isolated polynucleotide according to [any one of claims 6-12] claim 6.

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16. (Amended) A process for expressing a polynucleotide of [any one of claims 6 – 12] claim 6 comprising transforming a host cell with the expression vector comprising at least one of said polynucleotides and culturing said host cell under conditions sufficient for expression of any one of said polynucleotides.

17. (Amended) A vaccine composition comprising an effective amount of the polypeptide of [any one of claims 1 to 5] claim 1 and a pharmaceutically acceptable carrier.

18. (Amended) A vaccine composition comprising an effective amount of the polynucleotide of [any one of claims 6 to 12] claim 6 and a pharmaceutically effective carrier.

19. (Amended) The vaccine composition according to [either one of claims 17 or 18] claim 17 wherein said composition comprises at least one other *Neisseria meningitidis* antigen.

20. (Amended) An antibody immunospecific for the polypeptide or immunological fragment as claimed in [any one of claims 1 to 5] claim 1.

21. (Amended) A method of diagnosing a *Neisseria* infection, comprising identifying a polypeptide as claimed in [any one of claims 1 - 5] claim 1, or an antibody that is immunospecific for said polypeptide, present within a biological sample from an animal suspected of having such an infection.

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22. (Amended) Use of a composition comprising an immunologically effective amount of a polypeptide as claimed in [any one of claims 1 – 5] claim 1 in the preparation of a medicament for use in generating an immune response in an animal.

23. (Amended) Use of a composition comprising an immunologically effective amount of a polynucleotide as claimed in [any one of claims 6 - 12] claim 6 in the preparation of a medicament for use in generating an immune response in an animal.

24. (Amended) A therapeutic composition useful in treating humans with Neisseria meningitidis disease comprising at least one antibody directed against the polypeptide of [claims 1 – 5] claim 1 and a suitable pharmaceutical carrier.

**Novel *Neisseria meningitidis* compounds and  
anti-infection applications thereof**

5

**FIELD OF THE INVENTION**

This invention generally relates to novel *Neisseria meningitidis* (Nm) compounds,  
10 and to their anti-Nm infection applications. It more particularly relates to  
polynucleotides, herein referred to as Nm polynucleotide(s), polypeptides  
encoded by them (referred to herein as Nm polypeptide(s)), recombinant  
materials and methods for their production. In another aspect, the invention relates  
to methods for using such Nm polypeptides and Nm polynucleotides in anti-Nm  
15 infection applications, such as diagnostic, prophylactic and therapeutic uses  
thereof including vaccines against Nm infections. In a further aspect, the  
invention relates to diagnostic assays for detecting an Nm infection.

**BACKGROUND OF THE INVENTION**

20 *Neisseria meningitidis* (meningococcus) is a Gram negative bacterium frequently  
isolated from the human upper respiratory tract. It occasionally causes invasive  
bacterial diseases such as bacteremia and meningitis. The incidence of  
meningococcal disease shows geographical seasonal and annual differences  
(Schwartz, B., Moore, P.S., Broome, C.V.; Clin. Microbiol. Rev. 2 (Supplement),  
25 S18-S24, 1989). Most disease in temperate countries is due to strains of  
serogroup B, and varies in incidence from 1-10/100,000/year total population  
sometimes reaching higher values (Kaczmarek, E.B. (1997), Commun. Dis. Rep.  
Rev. 7: R55-9, 1995; Scholten, R.J.P.M., Bijlmer, H.A., Poolman, J.T. *et al.* Clin.  
Infect. Dis. 16: 237-246, 1993; Cruz, C., Pavez, G., Aguilar, E., *et al.* Epidemiol.

Infect. 105: 119-126, 1990).

- Epidemics dominated by serogroup A meningococci, mostly in central Africa, are encountered, sometimes reaching levels up to 1000/100.000/year (Schwartz, B., Moore, P.S., Broome, C.V. Clin. Microbiol. Rev. 2 (Supplement), S18-S24, 1989). Nearly all cases as a whole of meningococcal disease are caused by serogroup A, B, C, W-135 and Y meningococci and a tetravalent A, C, W-135, Y polysaccharide vaccine is available (Armand, J., Arminjon, F., Mynard, M.C., Lafaix, C., J. Biol. Stand. 10: 335-339, 1982).

10

The polysaccharide vaccines are currently being improved by way of chemical conjugating them to carrier proteins (Lieberman, J.M., Chiu, S.S., Wong, V.K., *et al.* JAMA 275 : 1499-1503, 1996).

- 15 A serogroup B vaccine is not available, since the B capsular polysaccharide was found to be nonimmunogenic, most likely because it shares structural similarity to host components (Wyle, F.A., Artenstein, M.S., Brandt, M.L. *et al.* J. Infect. Dis. 126: 514-522, 1972; Finne, J.M., Leinonen, M., Mäkelä, P.M. Lancet ii.: 355-357, 1983).

20

For many years efforts have been initiated and carried out to develop meningococcal outer membrane based vaccines (de Moraes, J.C., Perkins, B., Camargo, M.C. *et al.* Lancet 340: 1074-1078, 1992; Bjune, G., Hoiby, E.A. Gronnesby, J.K. *et al.* 338: 1093-1096, 1991). Such vaccines have demonstrated

25 efficacies from 57% - 85% in older children (>4 years) and adolescents, but none of them has demonstrated no significant efficacies in younger children/adults. These efficacies were further restricted to certain defined Nm strains, *i.e.* to the strain used to make the vaccine, and to related strains (*e.g.* of same electrophoretic type), without providing an efficient protection against most of the existing Nm

strains. Such vaccines does notably not provide an efficient protection against a wide range of Nm strains, such as every strain of at least one defined serogroup (such as serogroup B).

- 5 The frequency of *Neisseria meningitidis* infections has risen dramatically in the past few decades. This has been attributed to the emergence of multiply antibiotic resistant strains and an increasing population of people with weakened immune systems. It is no longer uncommon to isolate *Neisseria meningitidis* strains that are resistant to some or all of the standard antibiotics. This phenomenon has created
- 10 an unmet medical need and demand for new anti-microbial agents, vaccines, drug screening methods, and diagnostic tests for this organism.

## SUMMARY OF THE INVENTION

15

- The present invention relates to *Neisseria meningitidis* (Nm) polynucleotides and polypeptides, recombinant materials and methods for their production. In another aspect, the invention relates to methods for using such Nm polypeptides and polynucleotides, including prevention and treatment of Nm-related diseases.
- 20 In a further aspect, the invention relates to diagnostic assays for detecting Nm-related diseases and conditions associated with Nm infections, such as assays for detecting expression or activity of Nm polynucleotides or polypeptides.

- Various changes and modifications within the spirit and scope of the disclosed
- 25 invention will become readily apparent to those skilled in the art from reading the following descriptions and from reading the other parts of the present disclosure.



## DESCRIPTION OF THE INVENTION

The invention relates to *Neisseria meningitidis* (Nm) polypeptides and polynucleotides as described in greater detail below. In particular, the invention relates to Nm polynucleotides which cover the Nm genetic diversity and which correspond to Nm polypeptides of the outer membrane and/or the periplasma of Nm, and to the corresponding Nm polypeptide.

By "a polynucleotide which covers the Nm genetic diversity", it is herein meant that when assaying Nm Z2491, said polynucleotide can be observed as corresponding to at least an ORF fraction of more than 250 nucleotides, advantageously more than 500 nucleotides, preferably more than 750 nucleotides, but most preferably as corresponding to a complete ORF, and that said ORF is present in more than 70%, preferably in more than 80%, and more preferably in more than 90% of the strains of a panel of Nm strains chosen according to the MLST standard (multilocus sequence typing : see *e.g.* Maiden *et al.* 1998, Proc. Natl. Acad. Sci. 95 : 3140-3145) of which teaching is herein incorporated by reference. By "a polynucleotide corresponding to an ORF fraction, or a complete ORF" as above-mentioned, it is herein meant that said polynucleotide shows with said ORF fraction, or complete ORF, a sequence homology which is superior to about 85%, preferably to about 90%, more preferably to about 95%, and most preferably is a 100% homologue to said ORF fraction sequence, or ORF sequence. Such a panel may comprise Nm strains chosen serogroup A Nm strains, serogroup B Nm strains, serogroup C Nm strains, serogroup W135 Nm strains, and/or serogroup Y Nm strains. An advantageous Nm panel *e.g.* comprises Nm strains of the A, B, C, and W135 serogroups.

The invention relates especially to Nm compounds having the nucleotide and amino acid sequences set out in SEQ ID NO:1 to SEQ NO:90 (odd SEQ ID numbers for polynucleotides, even SEQ ID numbers for polypeptides), and are also illustrated in figures 1A to 45A (polynucleotides), and in figures 1B to 45B

(polypeptides). It is understood that sequences recited in the Sequence Listing below as "DNA" represent an exemplification of one embodiment of the invention, since those of ordinary skill will recognize that such sequences can be usefully employed in polynucleotides in general, including  
5 ribopolynucleotides.

Means for assaying the presence or absence of a polynucleotide in a bacterial strain are well known techniques to the person skilled in the art, and examples of such means comprise nucleic probe hybridization (see *e.g.* dot blot experiments in the below example 1). Said polynucleotide may correspond, or be part of a gene as  
10 well as, in certain Nm strains, to a pseudogene. Examples of such probes for said SEQ ID N°: 1-90 products include probes obtained by PCR amplification using the primers recited as SEQ ID N°: 97-116 and chromosomal DNA from Nm Z2491 as target DNA (see *e.g.* examples below and Table 2: SEQ ID N°97 and N°98 are nucleotidic forward and, respectively reverse primers for *dsbA*, SEQ ID  
15 N°99 and N°100 are nucleotidic forward and, respectively reverse primers for *fhuA*, SEQ ID N°101 and N°102 are nucleotidic forward and, respectively reverse primers for *rni5*, SEQ ID N°103 and N°104 are nucleotidic forward and, respectively reverse primers for *tolC*, SEQ ID N°105 and N°106 are nucleotidic forward and, respectively reverse primers for *rth17*, SEQ ID N°107 and N°108 are  
20 nucleotidic forward and, respectively reverse primers for *rth18*, SEQ ID N°109 and N°110 are nucleotidic forward and, respectively reverse primers for *rth19*, SEQ ID N°111 and N°112 are nucleotidic forward and, respectively reverse primers for *rth20*, SEQ ID N°113 and N°114 are nucleotidic forward and, respectively reverse primers for *rth21*, SEQ ID N°115 and N°116 are nucleotidic  
25 forward and, respectively reverse primers for *fhaB*). Appropriate PCR conditions for obtaining such probes with said primers and DNA template can be determined by the person skilled in the art ; as an example, these conditions may be : 1  $\mu\text{g}.\text{ml}^{-1}$  of template DNA ; reaction buffer (10 mM Tris-Cl, pH 8.0, 50 mM KCl, 1.5 mM  $\text{MgCl}_2$ , 0.001% gelatin) ; dATP, dCTP, dGTP and dTTP (200  $\mu\text{M}$  each);

dimethylsulfoxide (5%); forward and reverse primers (100 nM each) and Taq polymerase ; PCR incubation: 1 min at 94°C, 30 cycles of 1 min at 94° C, 1.5 min at 5°C below the T<sub>m</sub> of the oligonucleotide primers, and 2 min at 72° C followed by incubation for 5 min at 72° C.

5

It is understood that sequences recited herein as corresponding to any of SEQ ID N°:1-90 represent an exemplification of one embodiment of the invention since those of ordinary skill in the art will recognize that these sequences correspond to those identified on a panel of Nm strains constituted of Nm Z2491, Nm Z3524,  
10 Nm Z3842, Nm Z4667, Nm Z4707, Nm Z5005, Nm Z6466, Nm Z7176, Nm Z4662, Nm Z6904, Nm Z4259, Nm Z4673, Nm Z4683 (see "examples" below) as Nm ORF, and that variant, but homologue, *dsbA*, *phaB*, *fhuA*, *rni5*, *rth17*, *rth18*, *rth19*, *rth20*, *rth21*, *tolC*, sequences can be found in other Nm strains. Any appropriate technique can be implemented by the skilled person, *e.g.* sequencing  
15 the products which hybridize with said primers. Such variant sequences are thus encompassed by the present invention.

It is also understood that whereas the products of SEQ ID N°: 1-90 according to the invention are of first interest because of *inter alia* their Nm genetic diversity coverage, variant but homologue products which do not cover Nm genetic  
20 diversity on such a wide basis, can also be produced by the skilled person when desired. This means that the polypeptides and polynucleotides of the invention are candidates of first interest for construction or obtention of variant but homologue products which cover only one Nm serogroup, such as serogroup B, or which cover some but not all serogroups, such as serogroups B and A. Simple screening  
25 and/or trial and error tests can provide such variant sequences without undue burden. Such variant sequences are thus encompassed by the present invention.

### Polypeptides

In one aspect of the invention there are provided polypeptides of *Neisseria meningitidis* referred to herein as Nm polypeptides as well as biologically, diagnostically, prophylactically, clinically or therapeutically useful variants thereof, and compositions comprising the same.

5

The present invention further provides for:

(a) an isolated polypeptide which comprises an amino acid sequence which has at least 70% identity, preferably at least 80% identity, more preferably at least 90% identity, yet more preferably at least 95% identity, most preferably at least 97-99% or exact identity, to that of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90 ;

(b) a polypeptide encoded by an isolated polynucleotide comprising a polynucleotide sequence which has at least 70% identity, preferably at least 80% identity, more preferably at least 90% identity, yet more preferably at least 95% identity, even more preferably at least 97-99% or exact identity to SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, over the entire length of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89 respectively;

(c) a polypeptide encoded by an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide which has at least 70% identity, preferably at least 80% identity, more preferably at least 90% identity, yet more preferably at least 95% identity, even more preferably at least 97-99% or exact identity, to the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90.

The Nm polypeptide provided in SEQ ID NO : 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26 are the DsbA polypeptides from *Neisseria meningitidis* strains Z2491; Z3524, Z3842, Z4667, Z4707, Z5005, Z6466, Z7176, Z4662, Z6904, Z4259, 5 Z4673, Z4683 respectively.

The Nm polypeptide provided in SEQ ID NO : 28 is the polypeptide (348 aminoacids) corresponding to the 3' end fraction of FhaB from *Neisseria meningitidis* strains Z2491. 10

The Nm polypeptides provided in SEQ ID NO : 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52 are the FhuA polypeptides from *Neisseria meningitidis* strains Z2491, Z3524, Z3842, Z4259, Z4662; Z4667, Z4673, Z4683, Z4707, Z5005, Z6904, Z7176 respectively. 15

The Nm polypeptides provided in SEQ ID NO : 54 is the Rni5 polypeptide from *Neisseria meningitidis* strain Z2491.

The Nm polypeptides provided in SEQ ID NO : 56, 60, 62, 64 are the Rth17, 20 respectively Rth18, Rth19, Rth20, Rth21 polypeptides from *Neisseria meningitidis* strain Z2491.

The Nm polypeptides provided in SEQ ID NO : 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90 are the TolC polypeptides from *Neisseria meningitidis* strain Z2491, 25 Z3524, Z4707, Z3842, Z4259, Z4662, Z4667, Z4673, Z4683, Z5005, Z6466, Z6904, Z7176 respectively.

The Nm polypeptides of which ORF has some correspondance (i.e. significant hit in a computer program for sequence identity determination such as a standard

BLAST program, see also the below "definitions" section), though with no significant sequence identity/similarly, with an previously described ORF in another bacteria species have been named according to this previously known ORF. This is particularly the case of DsbA, FhaB, FhuA, Rth17 and TolC (see the below "examples"). The Nm polypeptides of which ORF has no significant hit with any gene of known function have been named according to the region plus a sequential number. This is particularly the case of Rni5, Rth18, Rth19, Rth20, Rth21.

A source of said Nm strains is given in the below "examples".

The invention also provides an immunogenic fragment of a Nm polypeptide, that is, a contiguous portion of the Nm polypeptide which has the same or substantially the same immunogenic activity as the polypeptide comprising the amino acid sequence of SEQ ID NO : 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90. That is to say, the fragment (if necessary when coupled to a carrier) is capable of raising an immune response which recognises the Nm polypeptide. Such an immunogenic fragment may include, for example, the Nm polypeptide lacking an N-terminal leader sequence, and/or a transmembrane domain and/or a C-terminal anchor domain. In a preferred aspect the immunogenic fragment according to the invention comprises substantially all of the extracellular domain of a polypeptide which has at least 70% identity, preferably at least 80% identity, more preferably at least 90% identity, yet more preferably at least 95% identity, most preferably at least 97-99% identity, to that of SEQ ID NO : 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90.

A fragment is a polypeptide having an amino acid sequence that is entirely the same as part but not all of any amino acid sequence of any polypeptide of the

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- Further preferred fragments include an isolated polypeptide comprising an amino acid sequence having at least 15, 20, 30, 40, 50 or 100 contiguous amino acids from the amino acid sequence of SEQ ID NO : 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90, or an isolated polypeptide comprising an amino acid sequence having at least 15, 20, 30, 40, 50 or 100 contiguous amino acids truncated or deleted from the amino acid sequence of SEQ ID NO : 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90.

- 30 Fragments of the polypeptides of the invention may be employed for producing

the corresponding full-length polypeptide by peptide synthesis; therefore, these fragments may be employed as intermediates for producing the full-length polypeptides of the invention.

- 5 Particularly preferred are variants in which several, 5-10, 1-5, 1-3, 1-2 or 1 amino acids are substituted, deleted, or added in any combination.

The polypeptides, or immunogenic fragments, of the invention may be in the form of the "mature" protein or may be a part of a larger protein such as a  
10 precursor or a fusion protein. It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification such as multiple histidine residues, or an additional sequence for stability during recombinant production. Furthermore, addition of exogenous polypeptide or lipid tail or  
15 polynucleotide sequences to increase the immunogenic potential of the final molecule is also considered.

In one aspect, the invention relates to genetically engineered soluble fusion proteins comprising a polypeptide of the present invention, or a fragment  
20 thereof, and various portions of the constant regions of heavy or light chains of immunoglobulins of various subclasses (IgG, IgM, IgA, IgE). Preferred as an immunoglobulin is the constant part of the heavy chain of human IgG, particularly IgG1, where fusion takes place at the hinge region. In a particular embodiment, the Fc part can be removed simply by incorporation of a  
25 cleavage sequence which can be cleaved with blood clotting factor Xa.

Furthermore, this invention relates to processes for the preparation of these fusion proteins by genetic engineering, and to the use thereof for drug screening, diagnosis and therapy. A further aspect of the invention also relates



5 The proteins may be chemically conjugated, or expressed as recombinant fusion proteins allowing increased levels to be produced in an expression system as compared to non-fused protein. The fusion partner may assist in providing T helper epitopes (immunological fusion partner), preferably T helper epitopes recognised by humans, or assist in expressing the protein (expression enhancer) at higher yields than the native recombinant protein. 10 Preferably the fusion partner will be both an immunological fusion partner and expression enhancing partner.

Fusion partners include protein D from *Haemophilus influenzae* and the non-structural protein from influenzae virus, NS1 (hemagglutinin). Another fusion partner is the protein known as LYTA. Preferably the C terminal portion of the molecule is used. Lyta is derived from *Streptococcus pneumoniae* which synthesize an N-acetyl-L-alanine amidase, amidase LYTA, (coded by the lytA gene {Gene, 43 (1986) page 265-272}) an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of E.coli C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at its amino terminus has been described {Biotechnology: 10, (1992) page 795-798}. It is possible to use the repeat portion of the Lyta molecule found in the C terminal end starting at residue 178, for example residues 188 - 305.

The present invention also includes variants of the aforementioned polypeptides, that is polypeptides that vary from the referents by conservative amino acid substitutions, whereby a residue is substituted by another with like characteristics. Typical such substitutions are among Ala, Val, Leu and Ile; among Ser and Thr; among the acidic residues Asp and Glu; among Asn and Gln; and among the basic residues Lys and Arg; or aromatic residues Phe and Tyr.

Polypeptides of the present invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

### Polynucleotides

It is an object of the invention to provide polynucleotides, herein designated Nm polynucleotides, which cover the Nm genetic diversity above and "examples" below for a definition of "Nm genetic diversity coverage"), and which correspond to outer membrane and/or periplasma Nm polypeptides. The present invention is particularly related to such Nm polynucleotides which comprises an ORF (open Reading Frame) coding for outer membrane and/or periplasma polypeptides.

In a particularly preferred embodiment of the invention the polynucleotide comprises a sequence set out in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89, or a variant thereof.

The Nm polynucleotides provided in SEQ ID NO : 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25 are the *dsbA* polynucleotides (complete ORF) from *Neisseria*

*meningitidis* strain Z2491, Z3524, Z3842, Z4667, Z4707, Z5055, Z6466, Z7176, Z4662, Z6904, Z4259, Z4673, Z4683 respectively.

5 The Nm polynucleotide provided in SEQ ID NO : 27 is the 3' end fraction (1047 nucleotides) of the *FhaB* ORF from *Neisseria meningitidis* strain Z2491.

The Nm polynucleotides provided in SEQ ID NO : 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51 are the *fhuA* polynucleotides (complete ORF) from *Neisseria meningitidis* strain Z2491, Z3524, Z3842, Z4259, Z4662, Z4667, Z4673, Z4683, 10 Z4707, Z5005, Z6904, Z7176 respectively.

The Nm polynucleotide provided in SEQ ID NO : 53 is the *rni5* polynucleotide (complete ORF) from *Neisseria meningitidis* strain Z2491.

15 The Nm polynucleotides provided in SEQ ID NO : 55, 57, 59, 61, 63 are the *rth17*, respectively *rth18*, *rth19*, *rth20*, *rth21* polynucleotides (complete ORF) from *Neisseria meningitidis* strain Z2491.

20 The Nm polynucleotides provided in SEQ ID NO : 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89 are the *tolC* polynucleotides (complete ORF) from *Neisseria meningitidis* strain Z2491, Z3524, Z4707, Z3842, Z4259, Z4662, Z4667, Z4673, Z4683, Z5005, Z6466, Z6904, Z7176 respectively.

25 As above explained for Nm polypeptides, Nm polynucleotides have been named according to the ORF with which some correspondance, though with no significant identity/similarity has been found in another species (*dsbA*, *fhaB*, *fhuA*, *rth17* and *tolC*), or, when no correspondance with a gene of known function has been found said Nm polynucleotides have been named according to the Nm region in which they have been located, plus a sequential number (*rni5*, *rth18*, *rth19*,

*rth20, rth21*).

As a further aspect of the invention there are provided isolated nucleic acid molecules encoding and/or expressing Nm polypeptides and polynucleotides, including, for example, unprocessed RNAs, ribozyme RNAs, mRNAs, cDNAs, genomic DNAs, B- and Z-DNAs. Further embodiments of the invention include biologically, diagnostically, prophylactically, clinically or therapeutically useful polynucleotides and polypeptides, and variants thereof, and compositions comprising the same.

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Another aspect of the invention relates to isolated polynucleotides, including at least one full length gene, that encodes a Nm polypeptide having a deduced amino acid sequence of SEQ ID NO : 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, and polynucleotides closely related thereto and variants thereof.

15

In another particularly preferred embodiment of the invention there is a Nm polypeptide from *Neisseria meningitidis* comprising or consisting of an amino acid sequence of SEQ ID NO : 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, or a variant thereof.

20

Using the information provided herein, such as a polynucleotide sequence set out in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, a polynucleotide of the invention encoding Nm polypeptide may be obtained using standard cloning and screening methods, such as those for cloning and sequencing chromosomal DNA fragments from bacteria using *Neisseria*

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*meningitidis* cells as starting material, followed by obtaining a full length clone. For example, to obtain a polynucleotide sequence of the invention, such as a polynucleotide sequence given in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, typically a library of clones of chromosomal DNA of *Neisseria meningitidis* in *E.coli* (such as a lambda DashII library) or some other suitable host is probed with a radiolabeled oligonucleotide, preferably a 17-mer or longer, derived from a partial sequence. Examples of such probes can be obtained by PCR amplification with the primers SEQ ID N°: 97-116 and with Nm Z2491 DNA as target DNA (see example 1 and Table 2 below).

Clones carrying DNA identical to that of the probe can then be distinguished using stringent hybridization conditions. By sequencing the individual clones thus identified by hybridization with sequencing primers designed from the original polypeptide or polynucleotide sequence it is then possible to extend the polynucleotide sequence in both directions to determine a full length gene sequence. Conveniently, such sequencing is performed, for example, using denatured double stranded DNA prepared from a plasmid clone. Suitable techniques are described by Maniatis, T., Fritsch, E.F. and Sambrook *et al.*, *MOLECULAR CLONING, A LABORATORY MANUAL*, 2nd Ed.; Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York (1989) (see in particular Screening By Hybridization 1.90 and Sequencing Denatured Double-Stranded DNA Templates 13.70). Direct genomic DNA sequencing may also be performed to obtain a full length gene sequence. Illustrative of the invention, each polynucleotide set out in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, was discovered in a DNA library derived from a *Neisseria meningitidis* panel (MLST).

Moreover, each DNA sequence set out in SEQ ID NO : 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89 corresponds to an open reading frame (ORF) encoding a protein having about the number of amino acid residues set forth in SEQ ID NO : 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, respectively with a deduced molecular weight that can be calculated using amino acid residue molecular weight values well known to those skilled in the art. The DNA sequence set out in SEQ ID N°: 27 corresponds to the 1047 3' end fraction of the ORF encoding a protein having about the number of amino acid residues set forth in SEQ ID NO: 28.

In a further aspect, the present invention provides for an isolated polynucleotide comprising or consisting of:

- 15 (a) a polynucleotide sequence which has at least 70% identity, preferably at least 80% identity, more preferably at least 90% identity, yet more preferably at least 95% identity, even more preferably at least 97-99% or exact identity to SEQ ID NO : 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, over the entire length of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89,
- 20 (b) a polynucleotide sequence encoding a polypeptide which has at least 70% identity, preferably at least 80% identity, more preferably at least 90% identity, yet more preferably at least 95% identity, even more preferably at least 97-99% or 100% exact, to the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90 over the entire length of SEQ ID NO : 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26,
- 25

28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90 respectively.

A polynucleotide encoding a polypeptide of the present invention may be obtained  
5 by a process which comprises the steps of screening an appropriate library under stringent hybridization conditions (for example, using a temperature in the range of 45 – 65°C and an SDS concentration from 0.1 – 1%) with a labeled or detectable probe consisting of or comprising the sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47,  
10 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, or a fragment thereof; and isolating a full-length gene and/or genomic clones containing said polynucleotide sequence.

The invention provides a polynucleotide sequence identical over its entire length  
15 to a coding sequence (open reading frame) in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89. Also provided by the invention is a coding sequence for a mature polypeptide or a fragment thereof, by itself as well as a coding sequence for a mature polypeptide or a  
20 fragment in reading frame with another coding sequence, such as a sequence encoding a leader or secretory sequence, a pre-, or pro- or prepro-protein sequence. The polynucleotide of the invention may also contain at least one non-coding sequence, including for example, but not limited to at least one non-coding 5' and 3' sequence, such as the transcribed but non-translated sequences,  
25 termination signals (such as rho-dependent and rho-independent termination signals), ribosome binding sites, Kozak sequences, sequences that stabilize mRNA, introns, and polyadenylation signals. The polynucleotide sequence may also comprise additional coding sequence encoding additional amino acids. For example, a marker sequence that facilitates purification of the fused polypeptide

can be encoded. In certain embodiments of the invention, the marker sequence is a hexa-histidine peptide, as provided in the pQE vector (Qiagen, Inc.) and described in Gentz *et al.*, *Proc. Natl. Acad. Sci., USA* 86: 821-824 (1989), or an HA peptide tag (Wilson *et al.*, *Cell* 37: 767 (1984), both of which may be useful in purifying polypeptide sequence fused to them. Polynucleotides of the invention also include, but are not limited to, polynucleotides comprising a structural gene and its naturally associated sequences that control gene expression.

The nucleotide sequence encoding Nm polypeptide of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90 may be identical to the polypeptide encoding sequence contained in Nm nucleotides of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, respectively. Alternatively it may be a sequence, which as a result of the redundancy (degeneracy) of the genetic code, also encodes the polypeptide of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90.

The term "polynucleotide encoding a polypeptide" as used herein encompasses polynucleotides that include a sequence encoding a polypeptide of the invention, particularly a *Neisseria meningitidis* polypeptide having an amino acid sequence set out in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90. The term also encompasses polynucleotides that include a single continuous region or discontinuous regions encoding the polypeptide (for example, polynucleotides interrupted by integrated phage, an integrated insertion sequence, an integrated vector sequence, an integrated transposon sequence, or due to RNA editing or genomic DNA reorganization)



together with additional regions, that also may contain coding and/or non-coding sequences.

The invention further relates to variants of the polynucleotides described herein  
5 that encode variants of a polypeptide having a deduced amino acid sequence of  
SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36,  
38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78,  
80, 82, 84, 86, 88, or 90. Fragments of polynucleotides of the invention may be  
used, for example, to synthesize full-length polynucleotides of the invention.

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Further particularly preferred embodiments are polynucleotides encoding Nm  
variants, that have the amino acid sequence of Nm polypeptide of SEQ ID NO: 2,  
4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46,  
48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88,  
15 or 90 in which several, a few, 5 to 10, 1 to 5, 1 to 3, 2, 1 or no amino acid residues  
are substituted, modified, deleted and/or added, in any combination. Especially  
preferred among these are silent substitutions, additions and deletions, that do not  
alter the properties and activities of Nm polypeptide.

20 Further preferred embodiments of the invention are polynucleotides that are at  
least 70% identical over their entire length to a polynucleotide encoding Nm  
polypeptide having an amino acid sequence set out in SEQ ID NO: 2, 4, 6, 8, 10,  
12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52,  
54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, and  
25 polynucleotides that are complementary to such polynucleotides. Alternatively,  
most highly preferred are polynucleotides that comprise a region that is at least  
80% identical over its entire length to a polynucleotide encoding Nm polypeptide  
and polynucleotides complementary thereto. In this regard, polynucleotides at  
least 90% identical over their entire length to the same are particularly preferred,

and among these particularly preferred polynucleotides, those with at least 95% are especially preferred. Furthermore, those with at least 97% are highly preferred among those with at least 95%, and among these those with at least 98% and at least 99% are particularly highly preferred, with at least 99% being the more preferred.

Preferred embodiments are polynucleotides encoding polypeptides that retain substantially the same biological function or activity as the mature polypeptide encoded by a DNA of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89.

In accordance with certain preferred embodiments of this invention there are provided polynucleotides that hybridize, particularly under stringent conditions, to Nm polynucleotide sequences, such as those polynucleotides in SEQ ID NO : 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89.

The invention further relates to polynucleotides that hybridize to the polynucleotide sequences provided herein. In this regard, the invention especially relates to polynucleotides that hybridize under stringent conditions to the polynucleotides described herein. As herein used, the terms "stringent conditions" and "stringent hybridization conditions" mean hybridization occurring only if there is at least 95% and preferably at least 97% identity between the sequences. A specific example of stringent hybridization conditions is overnight incubation at 42°C in a solution comprising: 50% formamide, 5x SSC (150mM NaCl, 15mM trisodium citrate), 50 mM sodium phosphate (pH7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 micrograms/ml of denatured, sheared salmon sperm DNA, followed by washing the hybridization support in 0.1x

SSC at about 65°C. Hybridization and wash conditions are well known and exemplified in Sambrook, *et al.*, Molecular Cloning: A Laboratory Manual, Second Edition, Cold Spring Harbor, N.Y., (1989), particularly Chapter 11 therein. Solution hybridization may also be used with the polynucleotide sequences provided by the invention.

The invention also provides a polynucleotide consisting of or comprising a polynucleotide sequence obtained by screening an appropriate library containing the complete gene for a polynucleotide sequence set forth in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89 under stringent hybridization conditions with a probe having the sequence of said polynucleotide sequence set forth in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89, or a fragment thereof; and isolating said polynucleotide sequence. Fragments useful for obtaining such a polynucleotide include, for example, probes and primers fully described elsewhere herein. An appropriate library may e.g. be a lambda DashII library containing Nm Z2491 ADN fragments from about 12 to about 23 kb.

As discussed elsewhere herein regarding polynucleotide assays of the invention, for instance, the polynucleotides of the invention, may be used as a hybridization probe for RNA, cDNA and genomic DNA to isolate full-length cDNAs and genomic clones encoding Nm polypeptides, and to isolate cDNA and genomic clones of other genes that have a high identity, particularly high sequence identity, to the Nm gene. Such probes generally will comprise at least 15 nucleotide residues or base pairs. Preferably, such probes will have at least 30 nucleotide residues or base pairs and may have at least 50 nucleotide residues or base pairs.

Particularly preferred probes will have at least 20 nucleotide residues or base pairs and will have less than 30 nucleotide residues or base pairs.

A coding region of a Nm gene may be isolated by screening using a DNA  
5 sequence provided in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25,  
27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67,  
69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89, to synthesize an oligonucleotide  
probe. A labeled oligonucleotide having a sequence complementary to that of a  
gene of the invention is then used to screen a library of cDNA, genomic DNA or  
10 mRNA to determine which members of the library the probe hybridizes to.

There are several methods available and well known to those skilled in the art  
to obtain full-length DNAs, or extend short DNAs, for example those based on  
the method of Rapid Amplification of cDNA ends (RACE) (see, for example,  
15 Frohman, *et al.*, *PNAS USA* 85: 8998-9002, 1988). Recent modifications of  
the technique, exemplified by the Marathon™ technology (Clontech  
Laboratories Inc.) for example, have significantly simplified the search for  
longer cDNAs. In the Marathon™ technology, cDNAs have been prepared  
from mRNA extracted from a chosen tissue and an 'adaptor' sequence ligated  
20 onto each end. Nucleic acid amplification (PCR) is then carried out to amplify  
the "missing" 5' end of the DNA using a combination of gene specific and  
adaptor specific oligonucleotide primers. The PCR reaction is then repeated  
using "nested" primers, that is, primers designed to anneal within the amplified  
product (typically an adaptor specific primer that anneals further 3' in the  
25 adaptor sequence and a gene specific primer that anneals further 5' in the  
selected gene sequence). The products of this reaction can then be analyzed by  
DNA sequencing and a full-length DNA constructed either by joining the  
product directly to the existing DNA to give a complete sequence, or carrying  
out a separate full-length PCR using the new sequence information for the

design of the 5' primer.

The polynucleotides and polypeptides of the invention may be employed, for example, as research reagents and materials for discovery of treatments of and  
5 diagnostics for Nm-related diseases, particularly human Nm-related diseases, as further discussed herein relating to polynucleotide assays.

The polynucleotides of the invention that are oligonucleotides derived from a sequence of SEQ ID NO : 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29,  
10 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89, may be used in the processes herein as described, but preferably for PCR, to determine whether or not the polynucleotides identified herein in whole or in part are transcribed in bacteria in infected tissue. It is recognized that such sequences will also have utility in  
15 diagnosis of the stage of infection and type of infection the pathogen has attained.

The invention also provides polynucleotides that encode a polypeptide that is the mature protein plus additional amino or carboxyl-terminal amino acids, or amino  
20 acids interior to the mature polypeptide (when the mature form has more than one polypeptide chain, for instance). Such sequences may play a role in processing of a protein from precursor to a mature form, may allow protein transport, may lengthen or shorten protein half-life or may facilitate manipulation of a protein for assay or production, among other things. As generally is the case *in vivo*, the  
25 additional amino acids may be processed away from the mature protein by cellular enzymes.

For each and every polynucleotide of the invention there is provided a polynucleotide complementary to it. It is preferred that these complementary

polynucleotides are fully complementary to each polynucleotide with which they are complementary.

A precursor protein, having a mature form of the polypeptide fused to one or more  
5 prosequences may be an inactive form of the polypeptide. When prosequences are removed such inactive precursors generally are activated. Some or all of the prosequences may be removed before activation. Generally, such precursors are called proproteins.

10 In addition to the standard A, G, C, T/U representations for nucleotides, the term "N" may also be used in describing certain polynucleotides of the invention. "N" means that any of the four DNA or RNA nucleotides may appear at such a designated position in the DNA or RNA sequence, except it is preferred that N is not a nucleic acid that when taken in combination with  
15 adjacent nucleotide positions, when read in the correct reading frame, would have the effect of generating a premature termination codon in such reading frame.

In sum, a polynucleotide of the invention may encode a mature protein, a mature  
20 protein plus a leader sequence (which may be referred to as a preprotein), a precursor of a mature protein having one or more prosequences that are not the leader sequences of a preprotein, or a preproprotein, which is a precursor to a proprotein, having a leader sequence and one or more prosequences, which generally are removed during processing steps that produce active and mature  
25 forms of the polypeptide.

In accordance with an aspect of the invention, there is provided the use of a polynucleotide of the invention for therapeutic or prophylactic purposes, in particular genetic immunization.

The use of a polynucleotide of the invention in genetic immunization will preferably employ a suitable delivery method such as direct injection of plasmid DNA into muscles (Wolff *et al.*, *Hum Mol Genet* (1992) 1: 363, Manthorpe *et al.*, *Hum. Gene Ther.* (1983) 4: 419), delivery of DNA  
5 complexed with specific protein carriers (Wu *et al.*, *J Biol Chem.* (1989) 264: 16985), coprecipitation of DNA with calcium phosphate (Benvenisty & Reshef, *PNAS USA*, (1986) 83: 9551), encapsulation of DNA in various forms of liposomes (Kaneda *et al.*, *Science* (1989) 243: 375), particle bombardment  
10 (Tang *et al.*, *Nature* (1992) 356:152, Eisenbraun *et al.*, *DNA Cell Biol* (1993) 12: 791) and *in vivo* infection using cloned retroviral vectors (Seeger *et al.*, *PNAS USA* (1984) 81: 5849).

#### 15 **Vectors, Host Cells, Expression Systems**

The invention also relates to vectors that comprise a polynucleotide or polynucleotides of the invention, host cells that are genetically engineered with  
20 vectors of the invention and the production of polypeptides of the invention by recombinant techniques. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the invention.

Recombinant polypeptides of the present invention may be prepared by processes  
25 well known in those skilled in the art from genetically engineered host cells comprising expression systems. Accordingly, in a further aspect, the present invention relates to expression systems that comprise a polynucleotide or polynucleotides of the present invention, to host cells which are genetically engineered with such expression systems, and to the production of polypeptides of

the invention by recombinant techniques.

For recombinant production of the polypeptides of the invention, host cells can be genetically engineered to incorporate expression systems or portions thereof or polynucleotides of the invention. Introduction of a polynucleotide into the host cell can be effected by methods described in many standard laboratory manuals, such as Davis, *et al.*, *BASIC METHODS IN MOLECULAR BIOLOGY*, (1986) and Sambrook, *et al.*, *MOLECULAR CLONING: A LABORATORY MANUAL*, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989), such as, calcium phosphate transfection, DEAE-dextran mediated transfection, transfection, microinjection, cationic lipid-mediated transfection, electroporation, transduction, scrape loading, ballistic introduction and infection.

Representative examples of appropriate hosts include bacterial cells, such as cells of streptococci, staphylococci, enterococci, *E. coli*, streptomyces, cyanobacteria, *Bacillus subtilis*, and *Neisseria meningitidis*; fungal cells, such as cells of a yeast, *Kluyveromyces*, *Saccharomyces*, a basidiomycete, *Candida albicans* and *Aspergillus*; insect cells such as cells of *Drosophila* S2 and *Spodoptera* Sf9; animal cells such as CHO, COS, HeLa, C127, 3T3, BHK, 293, CV-1 and Bowes melanoma cells; and plant cells, such as cells of a gymnosperm or angiosperm.

A great variety of expression systems can be used to produce the polypeptides of the invention. Such vectors include, among others, chromosomal-, episomal- and virus-derived vectors, for example, vectors derived from bacterial plasmids, from bacteriophage, from transposons, from yeast episomes, from insertion elements, from yeast chromosomal elements, from viruses such as baculoviruses, papova viruses, such as SV40, vaccinia viruses, adenoviruses, fowl pox viruses, pseudorabies viruses, picornaviruses, retroviruses, and alphaviruses and vectors derived from combinations thereof, such as those derived from plasmid and



bacteriophage genetic elements, such as cosmids and phagemids. The expression system constructs may contain control regions that regulate as well as engender expression. Generally, any system or vector suitable to maintain, propagate or express polynucleotides and/or to express a polypeptide in a host may be used for expression in this regard. The appropriate DNA sequence may be inserted into the expression system by any of a variety of well-known and routine techniques, such as, for example, those set forth in Sambrook *et al.*, *MOLECULAR CLONING, A LABORATORY MANUAL*, (*supra*).

In recombinant expression systems in eukaryotes, for secretion of a translated protein into the lumen of the endoplasmic reticulum, into the periplasmic space or into the extracellular environment, appropriate secretion signals may be incorporated into the expressed polypeptide. These signals may be endogenous to the polypeptide or they may be heterologous signals.

Polypeptides of the present invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, ion metal affinity chromatography (IMAC) is employed for purification. Well known techniques for refolding proteins may be employed to regenerate active conformation when the polypeptide is denatured during intracellular synthesis, isolation and or purification.

The expression system may also be a recombinant live microorganism, such as a virus or bacterium. The gene of interest can be inserted into the genome of a live recombinant virus or bacterium. Inoculation and *in vivo* infection with this live vector will lead to *in vivo* expression of the antigen and induction of

immune responses. Viruses and bacteria used for this purpose are for instance: poxviruses (*e.g.* vaccinia, fowlpox, canarypox), alphaviruses (Sindbis virus, Semliki Forest Virus, Venezuelan Equine Encephalitis Virus), adenoviruses, adeno-associated virus, picornaviruses (poliovirus, rhinovirus), herpesviruses (varicella zoster virus, *etc.*), Listeria, Salmonella, Shigella, BCG. These viruses and bacteria can be virulent, or attenuated in various ways in order to obtain live vaccines. Such live vaccines also form part of the invention.

#### **Diagnostic, Prognostic, Serotyping and Mutation Assays**

10

This invention is also related to the use of Nm polynucleotides and Nm polypeptides of the invention for use as diagnostic reagents. Detection of Nm polynucleotides, and/or polypeptides in an eukaryote, particularly a mammal, and especially a human, will provide a diagnostic method for diagnosis of Nm-related disease, staging of disease or response of an infectious organism to drugs. Eukaryotes, particularly mammals, and especially humans, particularly those infected or suspected to be infected with an organism comprising the Nm gene or protein, may be detected at the nucleic acid or amino acid level by a variety of well known techniques as well as by methods provided herein.

20

Polypeptides and polynucleotides for prognosis, diagnosis or other analysis may be obtained from a putatively infected and/or infected individual's bodily materials. Polynucleotides from any of these sources, particularly DNA or RNA, may be used directly for detection or may be amplified enzymatically by using PCR or any other amplification technique prior to analysis. RNA, particularly mRNA, cDNA and genomic DNA may also be used in the same ways. Using amplification, characterization of the species and strain of infectious or resident organism present in an individual, may be made by an analysis of the genotype of a selected polynucleotide of the organism. Deletions and insertions can be

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detected by a change in size of the amplified product in comparison to a genotype of a reference sequence selected from a related organism, preferably a different species of the same genus or a different strain of the same species. Point mutations can be identified by hybridizing amplified DNA to labeled Nm polynucleotide sequences. Perfectly or significantly matched sequences can be distinguished from imperfectly or more significantly mismatched duplexes by DNase or RNase digestion, for DNA or RNA respectively, or by detecting differences in melting temperatures or renaturation kinetics. Polynucleotide sequence differences may also be detected by alterations in the electrophoretic mobility of polynucleotide fragments in gels as compared to a reference sequence. This may be carried out with or without denaturing agents. Polynucleotide differences may also be detected by direct DNA or RNA sequencing. See, for example, Myers *et al.*, *Science*, 230: 1242 (1985). Sequence changes at specific locations also may be revealed by nuclease protection assays, such as RNase, V1 and S1 protection assay or a chemical cleavage method. See, for example, Cotton *et al.*, *Proc. Natl. Acad. Sci., USA*, 85: 4397-4401 (1985).

In another embodiment, an array of oligonucleotides probes comprising Nm nucleotide sequence or fragments thereof can be constructed to conduct efficient screening of, for example, genetic mutations, serotype, taxonomic classification or identification. Array technology methods are well known and have general applicability and can be used to address a variety of questions in molecular genetics including gene expression, genetic linkage, and genetic variability (see, for example, Chee *et al.*, *Science*, 274: 610 (1996)).

25

Thus in another aspect, the present invention relates to a diagnostic kit which comprises:

(a) at least one polynucleotide of the present invention, preferably the nucleotide sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23,

- 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89, or a fragment thereof; and/or
- (b) at least one nucleotide sequence complementary to that of (a); and/or
- (c) at least one polypeptide of the present invention, preferably the polypeptide
- 5 of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90, or a fragment thereof; and/or
- (d) at least one antibody to a polypeptide of the present invention, preferably to the polypeptide of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26,
- 10 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90.

It will be appreciated that in any such kit, (a), (b), (c) or (d) may comprise a substantial component. Such a kit will be of use in diagnosing a disease or

15 susceptibility to a Nm-related disease.

This invention also relates to the use of polynucleotides of the present invention as diagnostic reagents. Detection of a mutated form of a polynucleotide of the invention, preferably, SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27,

20 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89, which is associated with a Nm-related disease or pathogenicity will provide a diagnostic tool that can add to, or define, a diagnosis of said disease, a prognosis of a course of disease, a determination of a stage of disease, or a susceptibility to said disease, which results from under-

25 expression, over-expression or altered expression of the polynucleotide. Organisms, particularly infectious organisms, carrying mutations in such polynucleotide may be detected at the polynucleotide level by a variety of techniques, such as those described elsewhere herein.

Cells from an organism carrying mutations or polymorphisms (allelic variations) in a polynucleotide and/or polypeptide of the invention may also be detected at the polynucleotide or polypeptide level by a variety of techniques, to allow for serotyping, for example. For example, RT-PCR can be used to detect mutations in the RNA. It is particularly preferred to use RT-PCR in conjunction with automated detection systems, such as, for example, GeneScan. RNA, cDNA or genomic DNA may also be used for the same purpose, PCR. As an example, PCR primers complementary to a polynucleotide encoding Nm polypeptide can be used to identify and analyze mutations.

The invention further provides primers with 1, 2, 3 or 4 nucleotides removed from the 5' and/or the 3' end. These primers may be used for, among other things, amplifying Nm DNA and/or RNA isolated from a sample derived from an individual, such as a bodily material. The primers may be used to amplify a polynucleotide isolated from an Nm-infected individual, such that the polynucleotide may then be subject to various techniques for elucidation of the polynucleotide sequence. In this way, mutations in the polynucleotide sequence may be detected and used to diagnose and/or prognose the infection or its stage or course, or to serotype and/or classify the infectious agent.

The invention further provides a process for diagnosing infections caused by *Neisseria meningitidis*, comprising determining from a sample derived from an individual, such as a bodily material, an increased level of expression of polynucleotide having a sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89. Increased or decreased expression of a Nm polynucleotide can be measured using any one of the methods well known in the art for the quantitation of polynucleotides, such as, for example, amplification, PCR, RT-PCR, RNase protection, Northern

blotting, spectrometry and other hybridization methods.

In addition, a diagnostic assay in accordance with the invention for detecting over-expression of Nm polypeptide compared to normal control tissue samples may be used to detect the presence of an infection, for example. Assay techniques that can be used to determine levels of a Nm polypeptide, in a sample derived from a host, such as a bodily material, are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis, antibody sandwich assays, antibody detection and ELISA assays.

The polynucleotides of the invention may be used as components of polynucleotide arrays, preferably high density arrays or grids. These high density arrays are particularly useful for diagnostic and prognostic purposes. For example, a set of spots each comprising a different gene, and further comprising a polynucleotide or polynucleotides of the invention, may be used for probing, such as using hybridization or nucleic acid amplification, using a probes obtained or derived from a bodily sample, to determine the presence of a particular polynucleotide sequence or related sequence in an individual. Such a presence may indicate the presence of a pathogen, particularly *Neisseria meningitidis*, and may be useful in diagnosing and/or prognosing a Nm-related infection or a course of infection. A grid comprising a number of variants of the polynucleotide sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89, are preferred. Also preferred is a comprising a number of variants of a polynucleotide sequence encoding the polypeptide sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90.

### Antibodies

- The polypeptides and polynucleotides of the invention or variants thereof, or cells expressing the same can be used as immunogens to produce antibodies immunospecific for such polypeptides or polynucleotides respectively.

In certain preferred embodiments of the invention there are provided antibodies against Nm polypeptides or polynucleotides.

- Antibodies generated against the polypeptides or polynucleotides of the invention can be obtained by administering the polypeptides and/or polynucleotides of the invention, or epitope-bearing fragments of either or both, analogues of either or both, or cells expressing either or both, to an animal, preferably a nonhuman, using routine protocols. For preparation of monoclonal antibodies, any technique known in the art that provides antibodies produced by continuous cell line cultures can be used. Examples include various techniques, such as those in Köhler, G. and Milstein, C., *Nature* 256: 495-497 (1975); Kozbor *et al.*, *Immunology Today* 4: 72 (1983); Cole *et al.*, pg. 77-96 in *MONOCLONAL ANTIBODIES AND CANCER THERAPY*, Alan R. Liss, Inc. (1985).

20

- Techniques for the production of single chain antibodies (U.S. Patent No. 4,946,778) can be adapted to produce single chain antibodies to polypeptides or polynucleotides of this invention. Also, transgenic mice, or other organisms or animals, such as other mammals, may be used to express humanized antibodies immunospecific to the polypeptides or polynucleotides of the invention. preferably, said antibodies can bind to atleast one Nm polypeptide according to the invention in *in vivo* conditions, or in *in vitro* ones mimicking *in vivo* ones, but do not recognize the patient cells.

25

Alternatively, phage display technology may be utilized to select antibody genes with binding activities towards a polypeptide of the invention either from repertoires of PCR amplified v-genes of lymphocytes from humans screened for possessing anti-Nm or from naive libraries (McCafferty, *et al.*,  
5 (1990), *Nature* 348, 552-554; Marks, *et al.*, (1992) *Biotechnology* 10, 779-783). The affinity of these antibodies can also be improved by, for example, chain shuffling (Clackson *et al.*, (1991) *Nature* 352: 628).

The above-described antibodies may be employed to isolate or to identify clones  
10 expressing the polypeptides or polynucleotides of the invention to purify the polypeptides or polynucleotides by, for example, affinity chromatography.

Thus, among others, antibodies against Nm-polypeptide or Nm-polynucleotide may be employed to treat infections, particularly bacterial infections.

15 Polypeptide variants include antigenically, epitopically or immunologically equivalent variants form a particular aspect of this invention.

Preferably, the antibody or variant thereof is modified to make it less  
20 immunogenic in the individual. For example, if the individual is human the antibody may most preferably be "humanized," where the complementarity determining region or regions of the hybridoma-derived antibody has been transplanted into a human monoclonal antibody, for example as described in Jones *et al.* (1986), *Nature* 321, 522-525 or Tempest *et al.*, (1991)  
25 *Biotechnology* 9, 266-273.

#### **Antagonists and Agonists - Assays and Molecules**

Polypeptides and polynucleotides of the invention may also be used to assess the



binding of small molecule substrates and ligands in, for example, cells, cell-free preparations, chemical libraries, and natural product mixtures. These substrates and ligands may be natural substrates and ligands or may be structural or functional mimetics. See, e.g., Coligan *et al.*, *Current Protocols in Immunology* 5 1(2): Chapter 5 (1991).

The screening methods may simply measure the binding of a candidate compound to the polypeptide or polynucleotide, or to cells or membranes bearing the polypeptide or polynucleotide, or a fusion protein of the polypeptide by means of a label directly or indirectly associated with the candidate compound. Alternatively, the screening method may involve competition with a labeled competitor. Further, these screening methods may test whether the candidate compound results in a signal generated by activation or inhibition of the polypeptide or polynucleotide, using detection systems appropriate to the cells comprising the polypeptide or polynucleotide. Inhibitors of activation are generally assayed in the presence of a known agonist and the effect on activation by the agonist by the presence of the candidate compound is observed. Constitutively active polypeptide and/or constitutively expressed polypeptides and polynucleotides may be employed in screening methods for inverse agonists or inhibitors, in the absence of an agonist or inhibitor, by testing whether the candidate compound results in inhibition of activation of the polypeptide or polynucleotide, as the case may be. Further, the screening methods may simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide or polynucleotide of the present invention, to form a mixture, measuring Nm polypeptide and/or polynucleotide activity in the mixture, and comparing the Nm polypeptide and/or polynucleotide activity of the mixture to a standard. Fusion proteins, such as those made from Fc portion and Nm polypeptide, as hereinbefore described, can also be used for high-throughput screening assays

to identify antagonists of the polypeptide of the present invention, as well as of phylogenetically and/or functionally related polypeptides (see D. Bennett *et al.*, *J Mol Recognition*, 8:52-58 (1995); and K. Johanson *et al.*, *J Biol Chem*, 270(16):9459-9471 (1995)).

5

The polynucleotides, polypeptides and antibodies that bind to and/or interact with a polypeptide of the present invention may also be used to configure screening methods for detecting the effect of added compounds on the production of mRNA and/or polypeptide in cells. For example, an ELISA  
10 assay may be constructed for measuring secreted or cell associated levels of polypeptide using monoclonal and polyclonal antibodies by standard methods known in the art. This can be used to discover agents which may inhibit or enhance the production of polypeptide (also called antagonist or agonist, respectively) from suitably manipulated cells or tissues.

15

The invention also provides a method of screening compounds to identify those which enhance (agonist) or block (antagonist) the action of Nm polypeptides or polynucleotides, particularly those compounds that are bacteriostatic and/or bactericidal. The method of screening may involve high-throughput techniques.  
20 For example, to screen for agonists or antagonists, a synthetic reaction mix, a cellular compartment, such as a membrane, cell envelope or cell wall, or a preparation of any thereof, comprising Nm polypeptide and a labeled substrate or ligand of such polypeptide is incubated in the absence or the presence of a candidate molecule that may be a Nm agonist or antagonist. The ability of a  
25 candidate molecule to agonize or antagonize the Nm polypeptide is reflected in decreased binding of the labeled ligand or decreased production of product from such substrate. Molecules that bind gratuitously, *i.e.*, without inducing the effects of Nm polypeptide are most likely to be good antagonists. Molecules that bind well and, as the case may be, increase the rate of product production from

substrate, increase signal transduction, or increase chemical channel activity are agonists. Detection of the rate or level of, as the case may be, production of product from substrate, signal transduction, or chemical channel activity may be enhanced by using a reporter system. Reporter systems that may be useful in this regard include but are not limited to colorimetric, labeled substrate converted into product, a reporter gene that is responsive to changes in Nm polynucleotide or polypeptide activity, and binding assays known in the art.

Another example of an assay for Nm agonists is a competitive assay that combines an Nm compound according to the invention and a potential agonist with Nm compound binding molecules, recombinant Nm binding molecules, natural substrates or ligands, or substrate or ligand mimetics, under appropriate conditions for a competitive inhibition assay. Said Nm compound can be labeled, such as by radioactivity or a colorimetric compound, such that the number of Nm molecules bound to a binding molecule or converted to product can be determined accurately to assess the effectiveness of the potential antagonist.

Potential antagonists include, among others, small organic molecules, peptides, polypeptides and antibodies that bind to a polynucleotide and/or polypeptide of the invention and thereby inhibit or extinguish its activity or expression. Potential antagonists also may be small organic molecules, a peptide, a polypeptide such as a closely related protein or antibody that binds the same sites on a binding molecule, such as a binding molecule, without inducing activities induced by a Nm compound according to the invention, thereby preventing the action or expression of Nm polypeptides and/or polynucleotides by excluding Nm polypeptides and/or polynucleotides from binding.

Potential antagonists include a small molecule that binds to and occupies the binding site of the polypeptide thereby preventing binding to cellular binding

molecules, such that normal biological activity is prevented. Examples of small molecules include but are not limited to small organic molecules, peptides or peptide-like molecules. Other potential antagonists include antisense molecules (see Okano, *J. Neurochem.* 56: 560 (1991); *OLIGODEOXYNUCLEOTIDES AS ANTISENSE INHIBITORS OF GENE EXPRESSION*, CRC Press, Boca Raton, FL (1988), for a description of these molecules). Preferred potential antagonists include compounds related to and variants of NMEN.

In a further aspect, the present invention relates to genetically engineered soluble fusion proteins comprising a polypeptide of the present invention, or a fragment thereof, and various portions of the constant regions of heavy or light chains of immunoglobulins of various subclasses (IgG, IgM, IgA, IgE). Preferred as an immunoglobulin is the constant part of the heavy chain of human IgG, particularly IgG1, where fusion takes place at the hinge region. In a particular embodiment, the Fc part can be removed simply by incorporation of a cleavage sequence which can be cleaved with blood clotting factor Xa. Furthermore, this invention relates to processes for the preparation of these fusion proteins by genetic engineering, and to the use thereof for drug screening, diagnosis and therapy. A further aspect of the invention also relates to polynucleotides encoding such fusion proteins. Examples of fusion protein technology can be found in International Patent Application Nos. WO94/29458 and WO94/22914.

Each of the polynucleotide sequences provided herein may be used in the discovery and development of antibacterial compounds. The encoded protein, upon expression, can be used as a target for the screening of antibacterial drugs. Additionally, the polynucleotide sequences encoding the amino terminal regions of the encoded protein or Shine-Delgarno or other translation facilitating sequences of the respective mRNA can be used to construct

antisense sequences to control the expression of the coding sequence of interest.

The invention also provides the use of the polypeptide, polynucleotide, agonist  
5 or antagonist of the invention to interfere with the initial physical interaction  
between a pathogen or pathogens and a eukaryotic, preferably mammalian,  
host responsible for sequelae of infection. In particular, the molecules of the  
invention may be used: in the prevention of adhesion of bacteria, in particular  
10 gram positive and/or gram negative bacteria, to eukaryotic, preferably  
mammalian, extracellular matrix proteins on in-dwelling devices or to  
extracellular matrix proteins in wounds; to block bacterial adhesion between  
eukaryotic, preferably mammalian, extracellular matrix proteins and bacterial  
Nm proteins that mediate tissue damage and/or; to block the normal  
15 progression of pathogenesis in infections initiated other than by the  
implantation of in-dwelling devices or by other surgical techniques.

In accordance with yet another aspect of the invention, there are provided Nm  
agonists and antagonists of said Nm compounds according to the invention,  
preferably bacteristatic or bactericidal agonists and antagonists.

20

The antagonists and agonists of the invention may be employed, for instance, to  
prevent, inhibit and/or treat Nm-related diseases.

In a further aspect, the present invention relates to mimotopes of the  
25 polypeptide of the invention. A mimotope is a peptide sequence, sufficiently  
similar to the native peptide (sequentially or structurally), which is capable of  
being recognised by antibodies which recognise the native peptide; or is  
capable of raising antibodies which recognise the native peptide when coupled  
to a suitable carrier.

Peptide mimotopes may be designed for a particular purpose by addition, deletion or substitution of elected amino acids. Thus, the peptides may be modified for the purposes of ease of conjugation to a protein carrier. For example, it may be desirable for some chemical conjugation methods to include a terminal cysteine. In addition it may be desirable for peptides conjugated to a protein carrier to include a hydrophobic terminus distal from the conjugated terminus of the peptide, such that the free unconjugated end of the peptide remains associated with the surface of the carrier protein. Thereby presenting the peptide in a conformation which most closely resembles that of the peptide as found in the context of the whole native molecule. For example, the peptides may be altered to have an N-terminal cysteine and a C-terminal hydrophobic amidated tail. Alternatively, the addition or substitution of a D-stereoisomer form of one or more of the amino acids may be performed to create a beneficial derivative, for example to enhance stability of the peptide.

Alternatively, peptide mimotopes may be identified using antibodies which are capable themselves of binding to the polypeptides of the present invention using techniques such as phage display technology (EP 0 552 267 B1). This technique, generates a large number of peptide sequences which mimic the structure of the native peptides and are, therefore, capable of binding to anti-native peptide antibodies, but may not necessarily themselves share significant sequence homology to the native polypeptide.

## **Vaccines**

Another aspect of the invention relates to a method for inducing an immunological response in an individual, particularly a mammal, preferably humans, which comprises inoculating the individual with Nm polynucleotide

and/or Nm polypeptide, or a fragment or variant thereof, adequate to produce antibody and/ or T cell immune response to protect said individual from infection, particularly bacterial infection and most particularly *Neisseria meningitidis* infection. Also provided are methods whereby such immunological response slows bacterial replication. Yet another aspect of the invention relates to a method of inducing immunological response in an individual which comprises delivering to such individual a nucleic acid vector, sequence or ribozyme to direct expression of Nm polynucleotide and/or polypeptide, or a fragment or a variant thereof, for expressing Nm polynucleotide and/or polypeptide, or a fragment or a variant thereof *in vivo* in order to induce an immunological response, such as, to produce antibody and/ or T cell immune response, including, for example, cytokine-producing T cells or cytotoxic T cells, to protect said individual, preferably a human, from a Nm-related disease, whether that disease is already established within the individual or not. One example of administering the gene is by accelerating it into the desired cells as a coating on particles or otherwise. Such nucleic acid vector may comprise DNA, RNA, a ribozyme, a modified nucleic acid, a DNA/RNA hybrid, a DNA-protein complex or an RNA-protein complex. The expression system may also be a recombinant live micro-organism, such as a virus or a bacterium, which can be virulent, or attenuated in various ways in order to obtain live vaccines (see "Vectors, Host Cells, Expression Systems" above).

A further aspect of the invention relates to an immunological composition that when introduced into an individual, preferably a human, capable of having induced within it an immunological response, induces an immunological response in such individual to a Nm polynucleotide and/or Nm polypeptide encoded therefrom, wherein the composition comprises a recombinant Nm polynucleotide and/or polypeptide encoded therefrom and/or comprises DNA and/or RNA which encodes and expresses an antigen of said Nm

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- Also, provided by this invention are methods using the described polynucleotide or particular fragments thereof, which have been shown to encode non-variable regions of bacterial cell surface proteins, in polynucleotide constructs used in such genetic immunization experiments in animal models of infection with *Neisseria meningitidis*. Such experiments will be particularly useful for identifying protein epitopes able to provoke a prophylactic or therapeutic immune response. It is believed that this approach will allow for the subsequent preparation of monoclonal antibodies of particular value, derived from the requisite organ of the animal successfully resisting or clearing infection, for the development of prophylactic agents or therapeutic treatments of bacterial infection, particularly *Neisseria meningitidis* infection, in mammals, particularly humans.
- 15 The invention also includes a vaccine formulation which comprises an immunogenic recombinant polypeptide and/or polynucleotide of the invention together with a suitable carrier, such as a pharmaceutically acceptable carrier. The vaccine formulation according to the invention advantageously shows efficacies against at least one Nm serogroup, advantageously more than 2 Nm serogroups, preferably more than 3 Nm serogroups (e.g. Nm serogroups A, B, C and W135 and/or Y), most preferably against any Nm strain.
- 20 Since the polypeptides and polynucleotides may be broken down in the stomach, each is preferably administered parenterally, including, for example, administration that is subcutaneous, intramuscular, intravenous, or intradermal.
- 25 Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteristatic compounds and solutes which render the formulation isotonic with the bodily fluid, preferably the blood, of the individual; and aqueous and non-aqueous sterile suspensions which may include suspending agents or

thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials and may be stored in a freeze-dried condition requiring only the addition of the sterile liquid carrier immediately prior to use. Preferably, the vaccine formulation according to the invention is a anti-Nm meningitidis formulation.

The vaccine formulation of the invention may also include adjuvant systems for enhancing the immunogenicity of the formulation. Preferably the adjuvant system raises preferentially a TH1 type of response.

10

An immune response may be broadly distinguished into two extreme categories, being a humoral or cell mediated immune responses (traditionally characterised by antibody and cellular effector mechanisms of protection respectively). These categories of response have been termed TH1-type responses (cell-mediated response), and TH2-type immune responses (humoral response).

15

Extreme TH1-type immune responses may be characterised by the generation of antigen specific, haplotype restricted cytotoxic T lymphocytes, and natural killer cell responses. In mice TH1-type responses are often characterised by the generation of antibodies of the IgG2a subtype, whilst in the human these correspond to IgG1 type antibodies. TH2-type immune responses are characterised by the generation of a broad range of immunoglobulin isotypes including in mice IgG1, IgA, and IgM.

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It can be considered that the driving force behind the development of these two types of immune responses are cytokines. High levels of TH1-type cytokines tend to favour the induction of cell mediated immune responses to the given antigen, whilst high levels of TH2-type cytokines tend to favour the induction

of humoral immune responses to the antigen.

The distinction of TH1 and TH2-type immune responses is not absolute. In reality an individual will support an immune response which is described as being predominantly TH1 or predominantly TH2. However, it is often convenient to consider the families of cytokines in terms of that described in murine CD4 +ve T cell clones by Mosmann and Coffman (*Mosmann, T.R. and Coffman, R.L. (1989) TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. Annual Review of Immunology, 7, p145-173*). Traditionally, TH1-type responses are associated with the production of the INF- $\gamma$  and IL-2 cytokines by T-lymphocytes. Other cytokines often directly associated with the induction of TH1-type immune responses are not produced by T-cells, such as IL-12. In contrast, TH2- type responses are associated with the secretion of IL-4, IL-5, IL-6 and IL-13.

15

It is known that certain vaccine adjuvants are particularly suited to the stimulation of either TH1 or TH2 - type cytokine responses. Traditionally the best indicators of the TH1:TH2 balance of the immune response after a vaccination or infection includes direct measurement of the production of TH1 or TH2 cytokines by T lymphocytes *in vitro* after restimulation with antigen, and/or the measurement of the IgG1:IgG2a ratio of antigen specific antibody responses.

20

Thus, a TH1-type adjuvant is one which preferentially stimulates isolated T-cell populations to produce high levels of TH1-type cytokines when restimulated with antigen *in vitro*, and promotes development of both CD8+ cytotoxic T lymphocytes and antigen specific immunoglobulin responses associated with TH1-type isotype.

25

Adjuvants which are capable of preferential stimulation of the TH1 cell response are described in International Patent Application No. WO 94/00153 and WO 95/17209.

- 5 3 De-O-acylated monophosphoryl lipid A (3D-MPL) is one such adjuvant. This is known from GB 2220211 (Ribi). Chemically it is a mixture of 3 De-O-acylated monophosphoryl lipid A with 4, 5 or 6 acylated chains and is manufactured by Ribi Immunochem, Montana. A preferred form of 3 De-O-acylated monophosphoryl lipid A is disclosed in European Patent 0 689 454
- 10 B1 (SmithKline Beecham Biologicals SA).

Preferably, the particles of 3D-MPL are small enough to be sterile filtered through a 0.22micron membrane (European Patent number 0 689 454).

- 3D-MPL will be present in the range of 10mg - 100mg preferably 25-50mg per
- 15 dose wherein the antigen will typically be present in a range 2-50mg per dose.

- Another preferred adjuvant comprises QS21, an Hplc purified non-toxic fraction derived from the bark of Quillaja Saponaria Molina. Optionally this may be admixed with 3 De-O-acylated monophosphoryl lipid A (3D-MPL),
- 20 optionally together with an carrier.

The method of production of QS21 is disclosed in US patent No. 5,057,540.

- Non-reactogenic adjuvant formulations containing QS21 have been described
- 25 previously (WO 96/33739). Such formulations comprising QS21 and cholesterol have been shown to be successful TH1 stimulating adjuvants when formulated together with an antigen.

Further adjuvants which are preferential stimulators of TH1 cell response

include immunomodulatory oligonucleotides, for example unmethylated CpG sequences as disclosed in WO 96/02555.

Combinations of different TH1 stimulating adjuvants, such as those mentioned  
5 hereinaabove, are also contemplated as providing an adjuvant which is a preferential stimulator of TH1 cell response. For example, QS21 can be formulated together with 3D-MPL. The ratio of QS21 : 3D-MPL will typically be in the order of 1 : 10 to 10 : 1; preferably 1:5 to 5 : 1 and often substantially 1 : 1. The preferred range for optimal synergy is 2.5 : 1 to 1 : 1 3D-MPL:  
10 QS21.

Preferably a carrier is also present in the vaccine composition according to the invention. The carrier may be an oil in water emulsion, or an aluminium salt, such as aluminium phosphate or aluminium hydroxide.  
15

A preferred oil-in-water emulsion comprises a metabolisable oil, such as squalene, alpha tocopherol and Tween 80. In a particularly preferred aspect the antigens in the vaccine composition according to the invention are combined with QS21 and 3D-MPL in such an emulsion. Additionally the oil in  
20 water emulsion may contain span 85 and/or lecithin and/or tricaprylin.

Typically for human administration QS21 and 3D-MPL will be present in a vaccine in the range of 1mg - 200mg, such as 10-100mg, preferably 10mg - 50mg per dose. Typically the oil in water will comprise from 2 to 10%  
25 squalene, from 2 to 10% alpha tocopherol and from 0.3 to 3% tween 80. Preferably the ratio of squalene: alpha tocopherol is equal to or less than 1 as this provides a more stable emulsion. Span 85 may also be present at a level of 1%. In some cases it may be advantageous that the vaccines of the present invention will further contain a stabiliser.

Non-toxic oil in water emulsions preferably contain a non-toxic oil, e.g. squalane or squalene, an emulsifier, e.g. Tween 80, in an aqueous carrier. The aqueous carrier may be, for example, phosphate buffered saline.

5

A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil in water emulsion is described in WO 95/17210.

10 The present invention also provides a polyvalent vaccine composition comprising a vaccine formulation of the invention in combination with other antigens, in particular antigens useful for treating cancers, or autoimmune diseases. Such a polyvalent vaccine composition may include a TH-1 inducing adjuvant as hereinbefore described.

15 While the invention has been described with reference to certain Nm polypeptides and polynucleotides, it is to be understood that this covers fragments of the naturally occurring polypeptides and polynucleotides, and similar polypeptides and polynucleotides with additions, deletions or substitutions which do not substantially affect the immunogenic properties of  
20 the recombinant polypeptides or polynucleotides.

#### Compositions, kits and administration

In a further aspect of the invention there are provided compositions comprising a  
25 Nm polynucleotide and/or a Nm polypeptide for administration to a cell or to a multicellular organism.

The invention also relates to compositions comprising a polynucleotide and/or a polypeptides discussed herein or their agonists or antagonists. The polypeptides

and polynucleotides of the invention may be employed in combination with a non-sterile or sterile carrier or carriers for use with cells, tissues or organisms, such as a pharmaceutical carrier suitable for administration to an individual. Such compositions comprise, for instance, a media additive or a therapeutically effective amount of a polypeptide and/or polynucleotide of the invention and a pharmaceutically acceptable carrier or excipient. Such carriers may include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol and combinations thereof. The formulation should suit the mode of administration. The invention further relates to diagnostic and pharmaceutical packs and kits comprising one or more containers filled with one or more of the ingredients of the aforementioned compositions of the invention.

Polypeptides, polynucleotides and other compounds of the invention may be employed alone or in conjunction with other compounds, such as therapeutic compounds.

The pharmaceutical compositions may be administered in any effective, convenient manner including, for instance, administration by topical, oral, anal, vaginal, intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal or intradermal routes among others.

In therapy or as a prophylactic, the active agent may be administered to an individual as an injectable composition, for example as a sterile aqueous dispersion, preferably isotonic.

In a further aspect, the present invention provides for pharmaceutical compositions comprising a therapeutically effective amount of a polypeptide and/or polynucleotide, such as the soluble form of a polypeptide and/or polynucleotide of the present invention, agonist or antagonist peptide or small molecule compound,

in combination with a pharmaceutically acceptable carrier or excipient. Such carriers include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The invention further relates to pharmaceutical packs and kits comprising one or more containers filled with one or more of the ingredients of the aforementioned compositions of the invention. Polypeptides, polynucleotides and other compounds of the present invention may be employed alone or in conjunction with other compounds, such as therapeutic compounds. The present invention also provides for a therapeutic composition useful in treating animals or humans with *Neisseria meningitidis*-related disease, said composition comprising at least one antibody directed against a polypeptide according to the invention, and a suitable pharmaceutical carrier. Preferably, said antibody does not recognize the patient cells.

The composition will be adapted to the route of administration, for instance by a systemic or an oral route. Preferred forms of systemic administration include injection, typically by intravenous injection. Other injection routes, such as subcutaneous, intramuscular, or intraperitoneal, can be used. Alternative means for systemic administration include transmucosal and transdermal administration using penetrants such as bile salts or fusidic acids or other detergents. In addition, if a polypeptide or other compounds of the present invention can be formulated in an enteric or an encapsulated formulation, oral administration may also be possible. Administration of these compounds may also be topical and/or localized, in the form of salves, pastes, gels, solutions, powders and the like.

For administration to mammals, and particularly humans, it is expected that the daily dosage level of the active agent will be from 0.01  $\mu\text{g/kg}$  to 100  $\mu\text{g/kg}$ , preferably from 0.1 to 10  $\mu\text{g/kg}$ , typically around 1  $\mu\text{g/kg}$ . The physician in any event will determine the actual dosage which will be most suitable for an individual and will vary with the age, weight and response of the particular



individual. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

- 5 The dosage range required depends on the choice of peptide, the route of administration, the nature of the formulation, the nature of the subject's condition, and the judgment of the attending practitioner. Suitable dosages, however, are in the range of 0.1-100 µg/kg of subject.
- 10 A vaccine composition is conveniently in injectable form. Conventional adjuvants may be employed to enhance the immune response. A suitable unit dose for vaccination is 0.5-5 microgram/kg of antigen, and such dose is preferably administered 1-3 times and with an interval of 1-3 weeks. With the indicated dose range, no adverse toxicological effects will be observed with
- 15 the compounds of the invention which would preclude their administration to suitable individuals. A preferred vaccine composition is an anti-Nm meningitidis vaccine composition.

- Wide variations in the needed dosage, however, are to be expected in view of the
- 20 variety of compounds available and the differing efficiencies of various routes of administration. For example, oral administration would be expected to require higher dosages than administration by intravenous injection. Variations in these dosage levels can be adjusted using standard empirical routines for optimization, as is well understood in the art.

25

#### Sequence Databases, Sequences in a Tangible Medium, and Algorithms

Polynucleotide and polypeptide sequences form a valuable information resource with which to determine their 2- and 3-dimensional structures as well as to

identify further sequences of similar homology. These approaches are most easily facilitated by storing the sequence in a computer readable medium and then using the stored data in a known macromolecular structure program or to search a sequence database using well known searching tools, such as the GCG program package.

Also provided by the invention are methods for the analysis of character sequences or strings, particularly genetic sequences or encoded protein sequences. Preferred methods of sequence analysis include, for example, methods of sequence homology analysis, such as identity and similarity analysis, DNA, RNA and protein structure analysis, sequence assembly, cladistic analysis, sequence motif analysis, open reading frame determination, nucleic acid base calling, codon usage analysis, nucleic acid base trimming, and sequencing chromatogram peak analysis.

A computer based method is provided for performing homology identification. This method comprises the steps of: providing a first polynucleotide sequence comprising the sequence of a polynucleotide of the invention in a computer readable medium; and comparing said first polynucleotide sequence to at least one second polynucleotide or polypeptide sequence to identify homology.

A computer based method is also provided for performing homology identification, said method comprising the steps of: providing a first polypeptide sequence comprising the sequence of a polypeptide of the invention in a computer readable medium; and comparing said first polypeptide sequence to at least one second polynucleotide or polypeptide sequence to identify homology.

All publications and references, including but not limited to patents and patent

applications, cited in this specification are herein incorporated by reference in their entirety as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth. Any patent application to which this application claims priority is  
5 also incorporated by reference herein in its entirety in the manner described above for publications and references.

## DEFINITIONS

"Identity," as known in the art, is a relationship between two or more polypeptide sequences or two or more polynucleotide sequences, as the case may be, as determined by comparing the sequences. In the art, "identity" also means the degree of sequence relatedness between polypeptide or polynucleotide sequences, as the case may be, as determined by the match between strings of such sequences. "Identity" can be readily calculated by known methods, including but not limited to those described in (*Computational Molecular Biology*, Lesk, A.M., ed., Oxford University Press, New York, 1988; *Biocomputing: Informatics and Genome Projects*, Smith, D.W., ed., Academic Press, New York, 1993; *Computer Analysis of Sequence Data*, Part I, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; *Sequence Analysis in Molecular Biology*, von Heine, G., Academic Press, 1987; and *Sequence Analysis Primer*, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991; and Carillo, H., and Lipman, D., *SIAM J. Applied Math.*, 48: 1073 (1988). Methods to determine identity are designed to give the largest match between the sequences tested. Moreover, methods to determine identity are codified in publicly available computer programs. Computer program methods to determine identity between two sequences include, but are not limited to, the GAP program in the GCG program package (Devereux, J., et al., *Nucleic Acids Research* 12(1): 387 (1984)), BLASTP, BLASTN (Altschul, S.F. et al., *J. Molec. Biol.* 215: 403-410 (1990), and FASTA( Pearson and Lipman Proc. Natl. Acad. Sci. USA 85: 2444-2448 (1988). The BLAST family of programs is publicly available from NCBI and other sources (*BLAST Manual*, Altschul, S., et al., NCBI NLM NIH Bethesda, MD 20894; Altschul, S., et al., *J. Mol. Biol.* 215: 403-410 (1990). The well known Smith Waterman algorithm may also be used to determine identity.

Parameters for polypeptide sequence comparison include the following:

Algorithm: Needleman and Wunsch, J. Mol Biol. 48: 443-453 (1970)

Comparison matrix: BLOSSUM62 from Henikoff and Henikoff,  
Proc. Natl. Acad. Sci. USA. 89:10915-10919 (1992)

5 Gap Penalty: 8

Gap Length Penalty: 2

A program useful with these parameters is publicly available as the "gap"  
program from Genetics Computer Group, Madison WI. The aforementioned  
parameters are the default parameters for peptide comparisons (along with no  
10 penalty for end gaps).

Parameters for polynucleotide comparison include the following:

Algorithm: Needleman and Wunsch, J. Mol Biol. 48: 443-453 (1970)

Comparison matrix: matches = +10, mismatch = 0

15 Gap Penalty: 50

Gap Length Penalty: 3

Available as: The "gap" program from Genetics Computer Group, Madison  
WI. These are the default parameters for nucleic acid comparisons.

20 A preferred meaning for "identity" for polynucleotides and polypeptides, as  
the case may be, are provided in (1) and (2) below.

(1) Polynucleotide embodiments further include an isolated polynucleotide  
comprising a polynucleotide sequence having at least a 70, 80, 85, 90, 95, 97  
25 or 100% identity to the reference sequence of SEQ ID NO : 1, 3, 5, 7, 9, 11,  
13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53,  
55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89, wherein  
said polynucleotide sequence may be identical to the reference sequence of  
SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37,

39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89, or may include up to a certain integer number of nucleotide alterations as compared to the reference sequence, wherein said alterations are selected from the group consisting of at least one nucleotide  
 5 deletion, substitution, including transition and transversion, or insertion, and wherein said alterations may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among the nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence,  
 10 and wherein said number of nucleotide alterations is determined by multiplying the total number of nucleotides in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89, by the integer defining the percent identity divided by 100 and then subtracting that  
 15 product from said total number of nucleotides in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89:

$$n_n \leq x_n - (x_n \circ y),$$

20

wherein  $n_n$  is the number of nucleotide alterations,  $x_n$  is the total number of nucleotides in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89,  $y$  is 0.70 for 70%, 0.80 for 80%, 0.85 for  
 25 85%, 0.90 for 90%, 0.95 for 95%, 0.97 for 97% or 1.00 for 100%, and  $\circ$  is the symbol for the multiplication operator, and wherein any non-integer product of  $x_n$  and  $y$  is rounded down to the nearest integer prior to subtracting it from  $x_n$ . Alterations of a polynucleotide sequence encoding the polypeptide of SEQ ID

NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90, may create nonsense, missense or frameshift mutations in this coding sequence and thereby alter the polypeptide encoded by the polynucleotide following such alterations.

By way of example, a polynucleotide sequence of the present invention may be identical to the reference sequence of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89, that is it may be 100% identical, or it may include up to a certain integer number of nucleic acid alterations as compared to the reference sequence such that the percent identity is less than 100% identity. Such alterations are selected from the group consisting of at least one nucleic acid deletion, substitution, including transition and transversion, or insertion, and wherein said alterations may occur at the 5' or 3' terminal positions of the reference polynucleotide sequence or anywhere between those terminal positions, interspersed either individually among the nucleic acids in the reference sequence or in one or more contiguous groups within the reference sequence. The number of nucleic acid alterations for a given percent identity is determined by multiplying the total number of nucleic acids in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89, by the integer defining the percent identity divided by 100 and then subtracting that product from said total number of nucleic acids in SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89, or :

$$n_n \leq x_n - (x_n \circ y),$$

wherein  $n_n$  is the number of nucleic acid alterations,  $x_n$  is the total number of nucleic acids in SEQ-ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89,  $y$  is, for instance 0.70 for 70%, 0.80 for 80%, 0.85 for 85% etc.,  $*$  is the symbol for the multiplication operator, and wherein any non-integer product of  $x_n$  and  $y$  is rounded down to the nearest integer prior to subtracting it from  $x_n$ .

- (2) Polypeptide embodiments further include an isolated polypeptide comprising a polypeptide having at least a 70, 77, 80, 87, 89 or 100% identity to a polypeptide reference sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90, wherein said polypeptide sequence may be identical to the reference sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90, or may include up to a certain integer number of amino acid alterations as compared to the reference sequence, wherein said alterations are selected from the group consisting of at least one amino acid deletion, substitution, including conservative and non-conservative substitution, or insertion, and wherein said alterations may occur at the amino- or carboxy-terminal positions of the reference polypeptide sequence or anywhere between those terminal positions, interspersed either individually among the amino acids in the reference sequence or in one or more contiguous groups within the reference sequence, and wherein said number of amino acid alterations is determined by multiplying the total number of amino acids in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88,



or 90, by the integer defining the percent identity divided by 100 and then subtracting that product from said total number of amino acids in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90 :

$$n_a \leq x_a - (x_a \circ y),$$

wherein  $n_a$  is the number of amino acid alterations,  $x_a$  is the total number of amino acids in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90,  $y$  is 0.70 for 70%, 0.80 for 80%, 0.85 for 85%, 0.90 for 90%, 0.95 for 95%, 0.97 for 97% or 1.00 for 100%, and  $\circ$  is the symbol for the multiplication operator, and wherein any non-integer product of  $x_a$  and  $y$  is rounded down to the nearest integer prior to subtracting it from  $x_a$ .

By way of example, a polypeptide sequence of the present invention may be identical to the reference sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90, that is it may be 100% identical, or it may include up to a certain integer number of amino acid alterations as compared to the reference sequence such that the percent identity is less than 100% identity. Such alterations are selected from the group consisting of at least one amino acid deletion, substitution, including conservative and non-conservative substitution, or insertion, and wherein said alterations may occur at the amino- or carboxy-terminal positions of the reference polypeptide sequence or anywhere between those terminal positions, interspersed either individually among the amino acids in the reference

sequence or in one or more contiguous groups within the reference sequence. The number of amino acid alterations for a given % identity is determined by multiplying the total number of amino acids in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90, by the integer defining the percent identity divided by 100 and then subtracting that product from said total number of amino acids in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90 :

$$n_a \leq x_a - (x_a \bullet y),$$

wherein  $n_a$  is the number of amino acid alterations,  $x_a$  is the total number of amino acids in SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90,  $y$  is, for instance 0.70 for 70%, 0.80 for 80%, 0.85 for 85% etc., and  $\bullet$  is the symbol for the multiplication operator, and wherein any non-integer product of  $x_a$  and  $y$  is rounded down to the nearest integer prior to subtracting it from  $x_a$ .

"Individual(s)," when used herein with reference to an organism, means a multicellular eukaryote, including, but not limited to a metazoan, a mammal, an ovid, a bovid, a simian, a primate, and a human.

"Isolated" means altered "by the hand of man" from its natural state, *i.e.*, if it occurs in nature, it has been changed or removed from its original environment, or both. For example, a polynucleotide or a polypeptide naturally present in a living organism is not "isolated," but the same polynucleotide or polypeptide separated

from the coexisting materials of its natural state is "isolated", as the term is employed herein. Moreover, a polynucleotide or polypeptide that is introduced into an organism by transformation, genetic manipulation or by any other recombinant method is "isolated" even if it is still present in said organism, which organism may be living or non-living.

"Polynucleotide(s)" generally refers to any polyribonucleotide or polydeoxyribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA including single and double-stranded regions.

10

"Variant" refers to a polynucleotide or polypeptide that differs from a reference polynucleotide or polypeptide, but retains essential properties. A typical variant of a polynucleotide differs in nucleotide sequence from another, reference polynucleotide. Changes in the nucleotide sequence of the variant may or may not alter the amino acid sequence of a polypeptide encoded by the reference polynucleotide. Nucleotide changes may result in amino acid substitutions, additions, deletions, fusions and truncations in the polypeptide encoded by the reference sequence, as discussed below. A typical variant of a polypeptide differs in amino acid sequence from another, reference polypeptide. Generally, differences are limited so that the sequences of the reference polypeptide and the variant are closely similar overall and, in many regions, identical. A variant and reference polypeptide may differ in amino acid sequence by one or more substitutions, additions, deletions in any combination. A substituted or inserted amino acid residue may or may not be one encoded by the genetic code. A variant of a polynucleotide or polypeptide may be a naturally occurring such as an allelic variant, or it may be a variant that is not known to occur naturally. Non-naturally occurring variants of polynucleotides and polypeptides may be made by mutagenesis techniques or by direct synthesis.

"Disease(s)" means any disease caused by or related to infection by at least one *Neisseria meningitidis* strain, such as Nm meningitis.

In the below examples, reference is made to figures 1 to 50 which represent (for fig. 1 to 45: "A" letters for polynucleotidic sequences, "B" letters for polypeptidic ones) :

- 5 - figures 1 to 13 correspond *dsbA*/DsBA sequences obtained :
  - for allele 1 :
    - from Nm strain Z2491 (Fig. 1A, 1B),
    - from Nm strain Z3524 (Fig. 2A, 2B),
    - from Nm strain Z3842 (Fig. 3A, 3B),
    - 10 - from Nm strain Z4667 (Fig. 4A, 4B),
    - from Nm strain Z4707 (Fig. 5A, 5B),
    - from Nm strain Z5005 (Fig. 6A, 6B),
    - from Nm strain Z6466 (Fig. 7A, 7B),
    - from Nm strain Z7176 (Fig. 8A, 8B),
  - 15 - for allele 2 :
    - from Nm strain Z4662 (Fig. 9A, 9B),
    - from Nm strain Z6904 (Fig. 10A, 10B),
  - for allele 3 :
    - from Nm strain Z4259 (Fig. 11A, 11B),
    - 20 - from Nm strain Z4673 (Fig. 12A, 12B),
  - for allele 4:
    - from Nm strain Z4683 (Fig. 13A, 13B),
- figures 14A (1047 nucleotides) et 14B (348 aminoacids) correspond to the 3' end fraction of the *fhaB*, respectively FhaB, sequences obtained from Nm
- 25 strain Z2491,
  - figures 15 to 26 correspond to *fhuA*, FhuA sequences obtained from :
    - from Nm strain Z2491 (Fig. 15A, 15B),
    - from Nm strain Z3524 (Fig. 16A, 16B),
    - from Nm strain Z3842 (Fig. 17A, 17B),

- from Nm strain Z4259 (Fig. 18A, 18B),
- from Nm strain Z4662 (Fig. 19A, 19B),
- from Nm strain Z4667 (Fig. 20A, 20B),
- from Nm strain Z4673 (Fig. 21A, 21B),
- 5 - from Nm strain Z4683 (Fig. 22A, 22B),
- from Nm strain Z4707 (Fig. 23A, 234B),
- from Nm strain Z5005 (Fig. 24A, 24B),
- from Nm strain Z6904 (Fig. 25A, 25B),
- from Nm strain Z7176 (Fig. 26A, 26B),
- 10 - figures 27A et 27B correspond to *rni5*, respectively Rni5, sequences obtained from Nm Z2491,
- figures 28A et 28B correspond to *rth17*, respectively Rth17, sequences obtained from Nm Z2491,
- figures 29A et 29B correspond to *rth18*, respectively Rth18, sequences
- 15 obtained from Nm Z2491,
- figures 30A et 30B correspond to *rth19*, respectively Rth19, sequences obtained from Nm Z2491,
- figures 31A et 31B correspond to *rth20*, respectively Rth20, sequences obtained from Nm Z2491,
- 20 - figures 32A et 32B correspond to *rth21*, respectively Rth21, sequences obtained from Nm Z2491,
- figures 33 to 45 correspond to *tolC*/TolC sequences obtained :
  - for allele 1 :
    - from Nm strain Z2491 (Fig. 33A, 33B),
    - 25 - from Nm strain Z3524 (Fig. 34A, 34B),
  - for allele 2 :
    - from Nm strain Z4707 (Fig. 35A, 35B),
  - for allele 3 :
    - from Nm strain Z3842 (Fig. 36A, 36B),

- from Nm strain Z4259 (Fig. 37A, 37B),
- from Nm strain Z4662 (Fig. 38A, 38B),
- from Nm strain Z4683 (Fig. 39A, 39B),
- from Nm strain Z4673 (Fig. 40A, 40B),
- 5 - from Nm strain Z4667 (Fig. 41A, 41B),
- from Nm strain Z5005 (Fig. 42A, 42B),
- from Nm strain Z6466 (Fig. 43A, 43B),
- from Nm strain Z6904 (Fig. 44A, 44B),
- from Nm strain Z7176 (Fig. 45A, 45B),
- 10 - figure 46 illustrates the production of a knockout mutation of DsbA,
- figures 47A and 47B illustrate the immunofluorescence microscopy performed on wild-type and DsbA mutant bacteria with anti-recombinant DsbA antiserum (fig. 47A: wild type Nm 8013 ; fig. 47B: DsbA mutant 8013),
- figure 48 illustrates the bactericidal activity of anti-DsbA and the
- 15 corresponding pre-immune serum
- figure 49 illustrates the bactericidal activity of anti-DsbA antiserum against meningococci expressing an isogenic mutant lacking the protein DsbA,
- figure 50 illustrates Northern blot controls of the presence of DsbA in every MLST strains.

20

**EXAMPLE 1 :**

The examples below are carried out using standard techniques, which are well known and routine to those of skill in the art, except where otherwise described in

25 detail. The examples are illustrative, but do not limit the invention.

Strains of Nm were tested that represent the genetic diversity of this species according to MLST (Maiden *et al.* 1998, *supra*). .

Table 1

Nm strain Z number	Serological group	Clonal subgroup	ST
2491	A	IV-1	4
5005	A	I	1
3524	A	III	5
6466	A	IX	60
4662	B	groupe A4	8
3842	B	ET-5 (44/76)	32
7176	B	ET-5 (MC58)	74
4673	B	Lignée 3	41
4259	C	ET-37 (FAM18)	11
6904	W135	ET-37 (ROU)	11
4690	B	Autre	25
4683	B	Autre	30
4707	B	Autre	49
4667	B	Autre	48

5 Their MLST assignments were : ST1 (subgroup I, strain B40); ST2 (subgroup VI, Z6835); ST4 (subgroup IV-1, Z2491 (Sarkari *et al.*, 1994 Mol. Microbiol. 13 : 207-217)), ST5 (subgroup III, Z3524); ST8 (A4 cluster, BZ 10); ST11 (ET-37 complex, serogroup C: FAM18 ; serogroup W135: ROU (Pron *et al.*, 1997, J.



Infect. Dis. 176 : 1285-1292)); ST 25 (NG G40); ST30 (NG 4/88); ST32 (ET-5 complex, 44/76); ST41 (lineage 3, BZ 198); ST48 (BZ147); ST49 (297-0); ST60q (subgroup IX, 890592) et ST74 (ET-5 complex, MC58 (Virji *et al.*, 1995, Mol. Microbiol. 18 : 741-754)).

5

Nm were grown on GC agar (GCB, Difco), with the addition of Kellogg's defined supplement plus ferric nitrate (Kellog *et al.*, 1963) for 12 to 20 hours at 37°C in a moist atmosphere containing 5% CO<sub>2</sub>. Liquid media were GC-PO<sub>4</sub> (1.5 % Protease peptone number3 (Difco), 0.5 % NaCl, 30 mM potassium phosphate, pH 7.5) and GC-Hepes (like GC-PO<sub>4</sub> but potassium phosphate replaced by 30 mM Hepes, pH7.5) both supplemented as for the solid medium.

10

- Cloning of the polynucleotides coding for outer membrane and/or periplasma polypeptides in each Nm strains

15

By sequencing a Nm DNA library, such as a lambda DashII library containing 12-23 kb DNA fragments of Nm Z2491, nine ORF coding for outer membrane and/or periplasma polypeptides were cloned into *E. coli* and sequenced:

20

- *dsbA* (allele 1) SEQ ID N°: 1 (corresponding polypeptide: SEQ ID N°: 2),
- *fhuA* SEQ ID N°: 29 (corresponding polypeptide: SEQ ID N°: 30),
- *rni5* SEQ ID N°: 53 (corresponding polypeptide: SEQ ID N°: 54),
- *rth17* SEQ ID N°: 55 (corresponding polypeptide: SEQ ID N°: 56),
- *rth18* SEQ ID N°: 57 (corresponding polypeptide: SEQ ID N°: 58),
- *rth19* SEQ ID N°: 59 (corresponding polypeptide: SEQ ID N°: 60),
- *rth20* SEQ ID N°: 61 (corresponding polypeptide: SEQ ID N°: 62),
- *rth21* SEQ ID N°: 63 (corresponding polypeptide: SEQ ID N°: 64),
- *tolC* (allele 1) SEQ ID N°: 65 (corresponding polypeptide: SEQ ID N°: 66).

25

A further tenth ORF was identified as *fhaB*, but only a 3' end fraction of this ORF is herewith given: SEQ ID N° 27 (1047 nucleotides).

These sequences are illustrated by figures 1A and 1B, 14A and 14B, 27A and 27B, 28A and 28B, 29A and 29B, 30A and 30B, 31A and 31B, 32A and 32B, 33A and 33B, respectively, as above-recited (fig. number + A letter: polynucleotides; same fig. number + B letter: corresponding polypeptides).

From these 10 new products isolated from Nm Z2491, probes were constructed so as to determine whether these 9 new ORF and the complete ORF corresponding to said new *fhaB* ORF fraction are also present in the MLST Nm panel. Means for obtaining such probes include PCR amplification using the primers recited as SEQ ID N°: 97-116 and chromosomal DNA from Nm Z2491 as target DNA.

Appropriate PCR conditions for obtaining such probes with said primers and DNA template can be determined by the person skilled in the art; as an example, these conditions may be: 1  $\mu\text{g} \cdot \text{ml}^{-1}$  of template DNA; reaction buffer (10 mM Tris-Cl, pH 8.0, 50 mM KCl, 1.5 mM  $\text{MgCl}_2$ , 0.001% gelatin); dATP, dCTP, dGTP and dTTP (200  $\mu\text{M}$  each); dimethylsulfoxide (5%); forward and reverse primers (100 nM each) and Taq polymerase; PCR incubation: 1 min at 94°C, 30 cycles of 1 min at 94°C, 1.5 min at 5°C below the  $T_m$  of the oligonucleotide primers, and 2 min at 72°C followed by incubation for 5 min at 72°C. Primer sequences are given in the below Table 2, together with the size of the PCR products thus obtained:

Table 2

ORF	forward primer	5'-3' sequence	reverse primer	5'-3' sequence	size of PCR product (kb)
<i>fliA</i> B (probe, N-term)	<i>fliA</i> B-for	AAAGCACAGCACCATGGTTGCAGTAG CCGAAAC (SEQ ID N°115)	<i>fliA</i> B-rev	AGTGCTTTAGCCTCAATTACAGCAGCA CTGCC (SEQ ID N°116)	1.40
<i>rhl</i> 17	<i>rhl</i> 17-for	ACCGTGAGGCGGACTTGCC (SEQ ID N°107)	<i>rhl</i> 17-rev	TGGCCCGCATTCGCGGTTTAAAGCCGT CTTCG (SEQ ID N°108)	0.32
<i>rhl</i> 18 *	<i>rhl</i> 18-for	ATTTCGCGAGGGCGAACTGG (SEQ ID N°109)	<i>rhl</i> 18-rev	GCTTCGCAAAAGCCGACTTG (SEQ ID N°110)	0.40
<i>rhl</i> 19	<i>rhl</i> 19-for	GGCAACCGATTGCCATCATC (SEQ ID N°111)	<i>rhl</i> 19-rev	TTCCGTTTCAGACGGCTG (SEQ ID N°112)	0.27
<i>rhl</i> 20	<i>rhl</i> 20-for	AAGACCGTAAAAATGCAGGCG (SEQ ID N°113)	<i>rhl</i> 20-rev	TTCCGACTTTGCGGGGAGTG (SEQ ID N°114)	0.29
<i>rhl</i> 21	<i>rhl</i> 21-for	GGTTGGCTGCTTTCAAACGC (SEQ ID N°115)	<i>rhl</i> 21-rev	ATTAATATTTTGCCGCTTGAC (SEQ ID N°116)	0.28

\* primers for *rhl*18 are lying upstream of the start and downstream of the stop codon.

ORF	forward primer	5'-3' sequence	reverse primer	5'-3' sequence	size of PCR product (kb)
<i>tolC</i>	<i>tolC</i> -for	GCCTGACACTGACGCCCTATTGCA ACATGAAC (SEQ ID N°103)	<i>tolC</i> -rev	TACCGTGCTTGAGCCAGTTTCTGTTCTGC TTGG (SEQ ID N°104)	1.28
<i>dsbA</i>	<i>dsbA</i> -for	GCTTTGACTTCATTGACCCCTGTTGG CATTGGCC (SEQ ID N°97)	<i>dsbA</i> -rev	TATCCACCAACTGGTCAATCGTGGTCATA CCGG (SEQ ID N°99)	0.65
<i>fluA</i>	<i>fluA</i> -for	CCAGCTGATTATTGCTTCCTTCCC TGTTGCTG (SEQ ID N°99)	<i>fluA</i> -rev	ACCCGGCATAGAGTCCGACGCCCAATATT TTTG (SEQ ID N°100)	2.04
<i>rmlS</i>	<i>rmlS</i> -for	TGTTTCCCACCCAAACTTAC (SEQ ID N°101)	<i>rmlS</i> -rev	GTTCGTGGATGCAGACATAG (SEQ ID N°102)	0.36

These hybridization experiments performed under usual stringency conditions led to the conclusion that the nine new ORF and the complete ORF corresponding to the new *thaB* fraction, which were isolated from Nm Z2491, are present in every

5 Nm strain of the MLST panel. DNA dot blot hybridization was performed according to the DIG System Users Guide (Boehringer). One microliter containing 100 ng of denatured chromosomal DNA from each strain was spotted on nylon membranes (Hybond N, Amersham) and hybridized with DIG-labeled probes obtained by PCR amplification of each ORF. The hybridizations were performed

10 using high SDS buffer (Church buffer) at 37° C, and the last washing step was with 0.5 x SSC, 0.1% SDS at 50° C in order to allow approximately 30% mismatch. Positive hybridization signals were detected by chemiluminescence.

Some of these precise sequences corresponding to those initially isolated in Nm Z2491 are shown on (A letter for polynucleotides; B letter for corresponding

15 polypeptides):

- fig. 2A and 2B (Nm Z3524 ; SEQ ID N°3 and 4, respectively), fig. 3A and 3B (Nm Z4832 ; SEQ ID N°5 and 6, respectively), fig. 4A and 4B (Nm Z4667 ; SEQ ID N°7 and 8, respectively), fig. 5A and 5B (Nm Z4707 ; SEQ ID

20 N°9 and 10, respectively), fig. 6A and 6B (Nm Z5005 ; SEQ ID N°11 and 12, respectively), fig. 7A and 7B (Nm Z6466 ; SEQ ID N°13 and 14, respectively), fig. 8A and 8B (Nm Z7176 ; SEQ ID N°15 and 16, respectively), fig. 9A and 9B (Nm Z4662 ; SEQ ID N°17 and 18, respectively), fig. 10A and 10B (Nm Z6904 ; SEQ ID N°19 and 20, respectively), fig. 11A and 11B (Nm Z4259 ; SEQ ID N°21

25 and 22, respectively), fig. 12A and 12B (Nm Z4673 ; SEQ ID N°23 and 24, respectively), fig. 13A and 13B (Nm Z4683 ; SEQ ID N°25 and 26, respectively), for *dsbA* (respectively DsbA),

- fig. 16A and 16B (Nm Z3524 ; SEQ ID N°31 and 32, respectively), fig. 17A and 17B (Nm Z3842 ; SEQ ID N°33 and 34, respectively), fig. 18A and 18B

(Nm Z4259 ; SEQ ID N°35 and 36, respectively), fig. 19A and 19B (Nm Z4662 ; SEQ ID N°37 and 38, respectively), fig. 20A and 20B (Nm Z4667 ; SEQ ID N°39 and 40, respectively), fig. 21A and 21B (Nm Z4673 ; SEQ ID N°41 and 42, respectively), fig. 22A and 22B (Nm Z4683 ; SEQ ID N°43 and 44, respectively),  
5 fig. 23A and 23B (Nm Z4707 ; SEQ ID N°45 and 46, respectively), fig. 24A and 24B (Nm Z5005 ; SEQ ID N°47 and 48, respectively), fig. 25A and 25B (Nm Z6904 ; SEQ ID N°49 and 50, respectively), fig. 26A and 26B (Nm Z7176 ; SEQ ID N°51 and 52, respectively), for *fhuA* (respectively FhuA),

- fig. 34A and 34B (Nm Z3524 ; SEQ ID N°67 and 68, respectively), fig.  
10 35A and 35B (Nm Z4707 ; SEQ ID N°69 and 70, respectively), fig. 36A and 36B (Nm Z3842 ; SEQ ID N°71 and 72, respectively), fig. 37A and 37B (Nm Z4259 ; SEQ ID N°73 and 74, respectively), fig. 38A and 38B (Nm Z4662 ; SEQ ID N°75 and 76, respectively), fig. 39A and 39B (Nm Z4683 ; SEQ ID N°77 and 78, respectively), fig. 40A and 40B (Nm Z4673 ; SEQ ID N°79 and 80, respectively),  
15 fig. 41A and 41B (Nm Z4667 ; SEQ ID N°81 and 82, respectively), fig. 42A and 42B (Nm Z5005 ; SEQ ID N°83 and 84, respectively), fig. 43A and 43B (Nm Z6466 ; SEQ ID N°85 and 86, respectively), fig. 44A and 44B (Nm Z6904 ; SEQ ID N°87 and 88, respectively), fig. 45A and 45B (Nm Z7176 ; SEQ ID N°89 and 90, respectively), for *tolC* (respectively TolC).

20

Below is illustrated the high identity % observed for each of these compounds when comparing different Nm strains tested.

**Table 3**

Identity (%) between the *fhuA* DNA sequences (5 alleles) of the different Nm strains tested.

- 5 Only intact gene sequences have been compared (no pseudogenes)

	<b>Z4683</b>	<b>Z4259</b>	<b>Z6904</b>	<b>Z7176</b>
<b>Z2491</b>	97,2	96,9	96,2	98,7
<b>Z4683</b>		96,5	96,1	98,2
<b>Z4259</b>			98,9	98,0
<b>Z6904</b>				97,0

**Table 4**

Identity/similarly (%) between the FhuA proteins of the different Nm strains tested.

	<b>Z4683</b>	<b>Z4259</b>	<b>Z6904</b>	<b>Z7176</b>
<b>Z2491</b>	98,0 / 98,1	97,6 / 97,9	97,0 / 97,4	99,6
<b>Z4683</b>		96,7 / 97,2	96,9 / 97,2	98,4 / 98,6
<b>Z4259</b>			99,1 / 99,3	98,0 / 98,3
<b>Z6904</b>				97,4 / 97,9

10

**Table 5**

Identity (%) between the *dsbA* DNA sequences (4 alleles) of the different Nm strains tested.

	<b>Z4662</b>	<b>Z4259</b>	<b>Z4683</b>
<b>Z2491</b>	99,9	97,7	98,0
<b>Z4662</b>		97,6	97,8
<b>Z4259</b>			99,7

Nm strains which are below reported as linked by an "=" sign show an identical *dsbA* sequence.

Z2491=Z3524=Z3842=Z4667=Z4707=Z5005=Z6466=Z7176

Z4662=Z6904

5 Z4259=Z4673

Z4683

**Table 6**

10 Identity similarly (%) between the DsbA proteins (3 types) of the different Nm strains tested.

	<b>Z4259</b>	<b>Z4683</b>
<b>Z2491</b>	99,8 / 98,3	98,3 / 98,7
<b>Z4259</b>		99,6

Nm strains which are below reported as linked by an "=" sign show an identical *dsbA* sequence.

Z2491=Z3524=Z3842=Z4667=Z4707=Z5005=Z6466=Z7176=Z4662=Z6904

15 Z4259=Z4673

Z4683

**Table 7**

20 Identity (%) between the *tolC* DNA sequences (4 alleles) of the different Nm strains tested.

	<b>Z4259</b>	<b>Z4683</b>	<b>Z4707</b>
<b>Z2491</b>	99,8	99,7	99,9
<b>Z4259</b>		99,9	99,6
<b>Z4683</b>			99,6



Nm strains which are below reported as linked by an "=" sign show an identical *dsbA* sequence

Z2491=Z3524

Z4259=Z6904=Z3842=Z7176=Z6466=Z5005=Z4673=Z4667=Z4662

5 Z4683

Z4707 (pseudogene with a 4 pb deletion, which causes a stop codon after 16aa)

Identity / similarity between the TolC proteins (2 types) of the different NM strains tested.

10 Nm strains which are below reported as linked by an "=" sign show an identical *dsbA* sequence

Z2491 compared to Z4259 : identity = similarity = 99,8 %

Z2491=Z3524

Z4259=Z6904=Z3842=Z7176=Z6466=Z5005=Z4673=Z4667=Z4662=Z4683

15

The 45 polynucleotides herein illustrated thus appear as covering the Nm genetic diversity, as assessed by said MLST standard test. The person skilled in the art can further verify this Nm genetic diversity coverage by standard polynucleotide detection tests (e.g. with the help of said SEQ ID N°: 97-116 primers) performed in any other statistically significant Nm panel, and observe that said Nm polynucleotides are present in more than 90%, preferably more than 95%, more preferably in 100% of the Nm panel.

20

Each of said 45 Nm polynucleotides (ORF) were assessed for homologies to known proteins using standard BLAST programs as described in the below "definitions" section.

25

These results are illustrated in the below table 8.

**Table 8.** Open reading frames common to all Nm strains tested, and their correspondence (BLAST hits) with known proteins

ORF	Known protein						
	length (aa)	function	species	length (aa)	P	%identity / %similarity	Accession #
flaB	2015	filamentous hemagglutinin	B. pertussis	3591	1e-50	25/42	P12255
rth17	181	B precursor gene 25	phage SPP1	271	4e-04	28/39	X97918
ORFs with no significant hit (length in aa)							
rth18 (78), rth19 (155), rth20 (101), rth21 (115)							
tolC	467	outer membrane protein	E. coli	495	5e-20	23/40	P02930
flaA	703	ferrichrome iron receptor	E. coli	747	5e-26	23/40	P06971
dsbA	231	disulfide oxidoreductase	P. syringae	214	3e-18	28/47	AF036929
rnt5	230	MTH939, unknown function	Methanobacterium	188	1e-7	27/47	AE000868

The products according to the invention thus appear as novel compounds.

**EXAMPLE 2 : Efficacy of the products according to the invention such as DsbA (SEQ ID N°2) from *Neisseria meningitidis* for the production of anti-meningococcal vaccines**

In order to be considered as a good vaccine candidate against endemic meningococcal infections, a purified protein has to induce protective antibodies against a wide range of strains representative of the meningococcal population. Subsequently, to be considered as a vaccine candidate a protein has to be immunogenic, to be expressed on the outer membrane, and to induce protective antibodies. In this example (i) we demonstrate that DsbA is expressed in a set of NM strains representative of the meningococcal population by northern blots, (ii) we purified the protein and raised antibodies in rabbit, (iii) using this polyclonal antibody and immunofluorescence of whole bacteria we localised the protein on the outer membrane, (iv) we engineered a non polar mutation and using this mutant we demonstrate that the anti DsbA polyclonal antibody has a bactericidal activity against the wild type strain and not against the isogenic mutant. In this example, DsbA (SEQ ID N°2) was purified as a recombinant protein lacking the signal sequence associated with a hexahistidine tract only in order to facilitate purification. The same procedure can be implemented by the skilled person with any preparation of DsbA isolated directly from *Neisseria meningitidis*, by immunological or biochemical means and all other recombinant forms of the protein, or similarly with any product according to the invention.

**I. Northern Blot**

Controls of the presence of said recombinant DsbA in every MLST Nm strain have been performed by Northern blot analysis, as below detailed. These controls have confirmed

said DsbA covers Nm genetic diversity, as *e.g.* illustrated by figure 50 (Northern blots lanes are given in the below table 9). The marker used was the RNA molecular weight marker I, digoxigenin-labeled, from Boehringer, with 9 fragments, the sizes are indicated in the blot.

### Bacteria

**Table 9:**

lane	strain
1	Nm, serogroup A, subgroup IV-1
2	Nm, serogroup A, subgroup III
3	Nm, serogroup A, subgroup I
4	Nm, serogroup A, subgroup VI
5	Nm, serogroup A, subgroup IX
6	Nm, serogroup C, ET-37 complex, FAM18
7	Nm, serogroup W135, ET-37 complex, ROU
8	Nm, serogroup B, ET-5 complex, 44/76
9	Nm, serogroup B, ET-5 complex, MC58
10	Nm, serogroup B, Lineage 3
11	Nm, serogroup B, A4 cluster
12	Nm, serogroup B, ST25
13	Nm, serogroup B, ST30
14	Nm, serogroup B, ST48
15	Nm, serogroup B, ST49
16	Ng, FA1090

The *Neisseria meningitidis* strains chosen for RNA analysis represent the genetic diversity of this species according to multilocus sequence typing (MLST) (Maiden *et al.*, 1998).

#### Isolation of total RNA from *Neisseria*

Bacteria were grown on supplemented GC plates overnight at 37°C, 5% CO<sub>2</sub>, 95% humidity. Single colonies were inoculated in 5 ml supplemented GC medium and grown at 37°C, 180 rpm until an optical density of Klett 50 was reached. 4 ml bacterial culture was pelleted by centrifugation (5000 rpm, 10 min).

RNA isolation was performed using the RNAqueous Kit (Ambion, Austin, TX, USA) according to the manufacturer's protocol: The bacterial pellet was resuspended in 350 µl Lysis/Binding Solution. 400 µl 64% ethanol were added and mixed by repeated pipetting.

400 µl of the lysate/ethanol mixture were applied to a filter cartridge and centrifuged in a microcentrifuge for 1 min. The flow-through was discarded and the remaining lysate/ethanol mixture was centrifuged through the filter. The filter cartridge was once washed with 700 µl Wash Solution #1 and twice with 500 µl Wash Solution #2/3. The wash solutions were passed through the filter by centrifugation for 1 min; the last traces of wash solution were removed by 2 min centrifugation after the last washing step. The filter cartridge was transferred to a fresh collection tube and 60 µl of elution solution was added to the center of the filter. The cartridge was incubated in a heat block at 65°C for 10 min and the eluate was recovered by centrifugation for 1 min. This elution step was repeated with another 60 µl of elution solution. The concentration of the RNA was measured in a 1:10 dilution in elution solution. The average RNA yield was around 1.5 µg/µl. RNA was stored at -80°C.

#### RNA electrophoresis and transfer (Northern blot)

A 1% denaturing agarose gel was prepared by dissolving 0.5 g agarose in 40.5 ml H<sub>2</sub>O and cooling to 60°C. 5 ml 10 x MOPS buffer (0.2 M MOPS, pH 7.0, 0.05 M sodium-acetate, 0.01 M EDTA) and 4.5 ml formaldehyde (37%) were added and the gel was poured (gel size: 13 cm x 7.5 cm). 1 x MOPS was used as running buffer.

The RNA samples (ca. 3 µg per lane) were mixed with 4 volumes of gel loading solution

(supplied with the RNAqueous Kit) containing 10 µg/ml ethidium bromide. The samples were heated at 65°C for 10 min and immediately put on ice. The RNA was loaded and electrophoresis was performed at 5 V/cm until the bromophenol blue band had migrated two thirds of the length of the gel. The gel was photographed and washed for 10 min in

5 H<sub>2</sub>O to remove formaldehyde.

The RNA was transferred from the gel to Hybond N+ membrane (Amersham) by capillary transfer (Sambrook *et al.*, 1989) overnight using 20 x SSC (3 M NaCl, 0.3 M sodium citrate, pH 7.0) as transfer buffer.

10 The membrane was shortly washed with 2 x SSC and baked between Whatman 3MM filter paper for 30 min at 120°C.

#### Hybridization and detection

The RNA was detected using the DIG system (Boehringer Mannheim).

Labeling of the DNA probe:

15 Primers specific for the *dsbA* homolog of strain Z2491

(forward primer: 5'-GCTTTGACTTCATTGACCCTGTTGGCATTGGCC; (SEQ ID N°97)

reverse primer: 5'-TATCCACCAACTGGTCAATCGTGGTCATACCGG) SEQ ID N°98 were used in PCR amplification with DIG-labeled dUTP. Template chromosomal DNA of strain Z2491 was isolated as described (Sarkari *et al.*, 1994). The PCR reaction mixture contained template DNA (1 µg/ml); reaction buffer (10 mM Tris-Cl, pH 8.0, 50 mM KCl, 1.5 mM MgCl<sub>2</sub>, 0.01% gelatin); PCR DIG probe synthesis mix (200 µM dATP, dCTP, dGTP each, 190 µM dTTP, 10 µM digoxigenin-11-dUTP; Boehringer); forward and reverse primer (100 nM each) and Taq polymerase. The PCR reaction was incubated 1 min at 94°C, followed by 30 cycles of 1 min at 94°C, 1.5 min at 60°C and 2 min at 72°C followed by incubation for 5 min at 72°C. The labeled PCR product was purified using the Qiaquick PCR Purification Kit (Qiagen).

25 Hybridization conditions:

For prehybridization, the membrane was incubated for 2 h at 42°C with 20 ml of hybridization solution (High SDS Buffer: 7% SDS, 50% formamide, 5 x SSC, 2% Blocking Reagent (Boehringer), 50 mM sodium-phosphate, pH 7.0, 0.1% N-lauroylsarcosine) in a hybridization tube. This solution was replaced by 10 ml hybridization solution containing 250 ng of labeled probe. For denaturation, this solution was heated at 68°C for 10 min before adding. Hybridization was performed overnight at 42°C. After that, the membrane was washed 2 x 5 min at room temperature with 2 x SSC, 0.1% SDS and 2 x 30 min at 68°C with 0.5 x SSC, 0.1% SDS.

Detection by chemiluminescence:

After hybridization and washing, the membrane was equilibrated for 1 min in maleic acid buffer (100 mM maleic acid, 150 mM NaCl, pH 7.5). The membrane was blocked by gentle agitation in blocking solution (1% Blocking Reagent (Boehringer) in maleic acid buffer), followed by incubation with antibody solution (Anti-Digoxigenin, Fab fragments conjugated to alkaline phosphatase, 1:10000 in blocking solution) for further 30 min. The membrane was washed 2 x 15 min with maleic acid buffer and then equilibrated for 2 min in detection buffer (100 mM Tris-Cl, 100 mM NaCl, pH 9.5). The chemiluminescence substrate CSPD was diluted 1:100 in detection buffer. The membrane was treated with CSPD-solution for 5 min at room temperature in a sealed bag. After removing the CSPD-solution, the membrane was sealed again and incubated for 15 min at 37°C. The membrane was exposed to X-ray film for 1 h.

## II. Creation of an isogenic DsbA mutant of meningococci

Oligonucleotides were designed to amplify DNA fragments extending about 1 kilobase on either side of the first cysteine codon in *dsbA* (SEQ ID N°1) (This cysteine is immediately after the predicted site of proteolytic cleavage in the maturation of the protein DsbA). Oligonucleotides were designed such that a ligation of the two fragments recreates the DNA sequence of DsbA and some flanking sequence, with the exception that there is an

*EcoRI* restriction endonuclease site (an *EcoRI* site) in place of the DNA sequence coding for the predicted protease recognition site, the first cysteine codon is no longer present, there is an in-frame translational stop codon and the translational frame of the rest (3') of the gene is shifted by one base.

- 5 Oligonucleotides used to amplify the 5' end of the *DsbA* gene plus upstream sequence were:

b31331: GAACATGGATCCCGTCCACACACTTTACG  
(SEQ ID N°91)

b31311: GCGGCCGAATTCCAACAGGGTCAATGAAGT  
10 (SEQ ID N°92)

Oligonucleotides used to amplify the 3' end of *DsbA* plus downstream sequence were

b31312: CTGTTGGAATTCGGCCGCTTGTAGCAAACAGGCT  
(SEQ ID N°93)

- 15 b31313: TAGTACGGTACCGATTCACTTGGTGCTT  
(SEQ ID N°94)

In order to mutate the *dsbA* gene PCR amplification was performed using chromosomal DNA from strain 8013 (a serogroup C clinical isolate) as template.

- 20 Oligonucleotides b31311 and b31312 contain complementary sequences, such that mixture of the two PCR products in the presence of the two 'external' oligonucleotides b31331 and b31313 results in 'PCR ligation' forming the DNA fragment extending from the position of b31331 to that of b31313, and including the modifications described above. This fragment was cleaved with the enzymes *Bam*HI and *Kpn*I and cloned into appropriately cleaved vector pBluescript II SK(+), which was then propagated in *E. coli* DH5 $\alpha$ . This construction was linearised by digestion with *EcoRI*. Into the *EcoRI* site was inserted a resistance cassette containing a gene encoding resistance to erythromycin and two neisserial uptake sequences (GCCGTCTGAA) which have been shown to be necessary for efficient transformation of Nm [Goodman, S. D., and Scocca, J. J. (1988).
- 25



Identification and arrangement of the DNA sequence recognized in specific transformation of *Neisseria gonorrhoeae*. *Proc. Natl. Acad. Sci. USA* 85, 6982-6986]. The plasmid containing the *dsbA* gene interrupted by the erythromycin resistance cassette was used to transform Nm to erythromycin resistance, selecting on 2 µg/ml erythromycin.

5 Chromosomal DNA, prepared from a selected transformant strain was used to back transform the parental strain 8013 (serogroup C ; see Nassif X., D. Puaoli, and M. So. Transposition of Tn1545-\*3 in the pathogenic *Neisseriae*: a genetic tool for mutagenesis, *Journal of Bacteriology*, 1991, 173, 2147-2154) and several hundred transformant colonies were taken to give a statistically homogeneous genetic background.

10 The transformant strain was tested by western blot in order to show that it no longer expressed the protein DsbA, using either rabbit anti-whole cell (strain Z5463) or anti-DsbA antiserum.

The overall strategy is illustrated by figure 46 which shows the production of a knockout mutation of DsbA. On this figure, ORF are shown as arrows (note that the sequence shown is that of Z2491 and that strain 8013 does not contain the ORF *rei1* ; the PCR product b31331-31311 is correspondingly shorter). The position of the oligonucleotide primers are shown as small arrows. PCR products are shown as shaded boxes. The two PCR products were ligated (fig. 46a) and cloned into the vector pBluescript. After linearisation of the plasmid by cleavage with *EcoRI*, the resistance cassette (dark grey) was inserted (fig. 46b). This construction was used to transform Nm to erythromycin resistance (fig. 46c), thus replacing the wild-type *dsbA* gene with that interrupted with the resistance cassette.

15

20

### III. Cloning and expression of DsbA for use in production of anti-DsbA antiserum

25 **Overview of cloning strategy.** The antigen DsbA is predicted to be a lipoprotein, whose lipophilic signal sequence is cleaved to leave an N-terminal cysteine residue which is subsequently modified by the addition of (a) fatty acid molecule(s) for anchorage in the

outer membrane [Pugsley, A. P. (1993). The complete general secretory pathway in Gram-negative bacteria. *Microbiol. Rev.* 57, 50-108]. This signal sequence is not present in the mature protein. After cloning and overexpression of the gene, if the protein were exported in large quantities to the outer membrane of the host *E. coli* it could prove toxic for the bacteria. On the basis of these considerations, the gene was not cloned in its entirety, but only the sequence coding for the predicted mature protein was cloned and expressed. In order to minimise the metabolic load on the host bacteria, the (codon for the) N-terminal cysteine of the mature protein was replaced by a (codon for a) serine.

Primers were designed in order to amplify DNA corresponding to the predicted mature protein DsbA and to allow subsequent ligation into an expression vector which links the protein at its C-terminal end to a hexahistidine tract (His-tag) in order to facilitate subsequent purification, using a nickel affinity column.

#### Oligonucleotides

b31316b (GCTTGTGGTACCATATGAGCAAACAGGCTGAAACCAGT ;

SEQ ID N°95)

and b31317 (TCAATCCTCGAGTTGCGGCTTTTCTGCTCTT ;

SEQ ID N°96) were designed to amplify a fragment from the chromosome of Nm strain Z2491. Oligonucleotide b31316b contains a recognition site for the restriction endonuclease *NdeI* (CATATG) allowing the fragment to be cloned into the expression vector pET20b(+) (Novagen R&D systems). The latter half of this site specifies the amino acid methionine, which is the N-terminal amino acid of the expressed protein. This is followed by a codon specifying serine (which was chosen to replace the N-terminal cysteine of the mature protein) and subsequently by bases corresponding to the gene sequence. The oligonucleotide b31317 causes the replacement of the gene's natural stop codon with the first three bases of an *XhoI* site (CTCGAG), which allows an in frame link to the expression vector's hexahistidine encoding sequence. Translation is terminated after the hexahistidine by a stop codon in the vector.

Overview of strategy for overexpression of the cloned protein. The expression vector takes advantage of an *NdeI* site to allow insertion of a coding DNA sequence such that the second half of this site (ATG) is recognised by the ribosome as the first amino acid of the recombinant protein to be expressed. Since cleavage by the enzyme *NdeI* is particularly inefficient near the extremity of a PCR product, it is easier to clone the PCR product using another method (either using a site incorporated into the oligonucleotide 5' to the *NdeI* site, by 'TA cloning', or by enzymatically blunting the fragment and ligating into a 'blunt-ended' restriction enzyme site) then excise the coding fragment using the enzymes *NdeI* and that at the 3' end of the gene). This fragment is then ligated into the expression vector and the resulting plasmid grown in *E. coli* strain DH5 $\alpha$ , which is highly transformable and will not be harmed by the expression of the potentially toxic foreign protein since it is incapable of initiating transcription from the T7 RNA polymerase promoter in the expression vectors. Plasmid isolated from DH5 $\alpha$  is then used to transform (at high efficiency) *E. coli* strain BL21(DE3). This strain contains a gene for T7 RNA polymerase preceded by the *lac* promoter and hence inducible by isopropyl b-D-thiogalactoside (IPTG). Addition of IPTG to the culture medium induces the transcription of the T7 RNA polymerase gene. The recombinant protein gene is read by the T7 RNA polymerase, and the transcript translated to overproduce the recombinant protein.

**Cloning of the DsbA gene.** The PCR products from b31316b and b31317 using chromosomal DNA as template were blunted (using the Klenow fragment of *E. coli* DNA polymerase and T4 phage polynucleotide kinase in the presence of the four deoxynucleotide triphosphates and ATP) and ligated into the *SmaI* site of plasmid pUC18. The ligation mixtures were used to transform *E. coli* DH5 $\alpha$ , and the resulting plasmid were cleaved with *NdeI* and *XhoI*. The liberated fragment was gel purified and ligated into the expression vector pET-20b(+). The ligation mixture was used to transform *E. coli* DH5 $\alpha$ , then plasmid was isolated and used to transform BL21(DE3). Individual colony isolates were screened for production of the recombinant protein by SDS-PAGE. One

isolate was chosen for subsequent use in protein purification. This isolate was designated 2g:

Name	<i>E. coli</i> strain	construction	expressed protein
2g	BL21(DE3)	pET20b(+):PCR product b31316b-b31317	DsbA-(C-terminal his tag)

**Purification of the recombinant proteins.** Recombinant DsbA protein was purified using an affinity column produced with Poly-His protein purification resin. Bacteria (20 to 50 isolated colonies of overnight growth on LB agar containing 100 mg/ml of ampicillin) were inoculated into 500 ml of LB medium containing 100 mg/ml of ampicillin and incubated at 37°C in a conical flask with orbital shaking to maintain aeration. When the OD at 600 nm of the culture had reached between 0.4 and 0.5, the expression of the protein was induced by addition of IPTG to 2 mM. Growth was continued for a further 2 hours, then the bacteria were harvested by centrifugation at 3500 x g for 25 minutes. The pellets were sonicated (three times 5 minutes, on ice) in 10 ml of PBS to break the cells. The suspension was centrifuged at 15000 x g and the supernatant taken. For purification, 5 ml of the supernatant was passed through a column made from 1 ml of 'poly-His protein purification resin' (Boehringer Mannheim). The column was washed with 5 ml of PBS containing 10 mM imidazole, then 5 ml of PBS/20 mM imidazole. The recombinant DsbA protein was eluted in PBS/50 mM imidazole, then PBS/500 mM imidazole. Fractions containing pure recombinant DsbA (by SDS-PAGE analysis) were pooled and dialysed against PBS. Stocks containing recombinant DsbA at 100 µg/ml were stored at -80°C.

#### IV. Immunisation of a rabbit with recombinant DsbA.

New Zealand white rabbits were immunised three times at intervals of 15 days with 100 µg of recombinant DsbA (preparation 2g).

1st immunisation 2 ml of antigen '2g' in PBS:Freund's complete adjuvant (1:1)

2nd immunisation 2 ml of antigen '2g' in PBS:Freund's incomplete adjuvant

(1:1)

3rd immunisation 2 ml of antigen '2g' in PBS:Freund's incomplete adjuvant

(1:1)

Blood was taken from the rabbits 3 weeks after the third immunisation and allowed to clot overnight. Serum was separated from the clot by centrifugation and stored in aliquots at -80C.

## V. Immunofluorescence staining of meningococci

Meningococci were grown for 18 hours on GCB-agar (Difco), then resuspended in PBS.

- 5 Drops of suspension were immediately placed on glass microscope slides and allowed to dry at 45°C. The bacteria were fixed to the slide by adding methanol and allowing to evaporate (twice). The bacteria were pretreated with PBS containing 1% gelatin, then reacted with the primary antibody (1/1000 dilution of the rabbit anti-recombinant DsbA in PBS/gelatin) for 30 minutes at room temperature. The slides were washed twice for 2
- 10 minutes in an excess of PBS, then reacted with 1/200 dilutions the secondary antibody in PBS/gelatin (sheep anti-rabbit immunoglobulin G-Cy3-conjugate) for 30 minutes at room temperature. Slides were washed three times for 5 minutes in an excess of PBS, then the bacteria were counterstained with DAPI (1 µg/ml in PBS/10% methanol) and rinsed twice in PBS. The slides were allowed nearly to dry, then the mounting fluid 'morviol' (Sigma)
- 15 was added to the bacteria and cover slips were fixed in place. The bacteria and fixed antibodies were visualised by ultraviolet and light microscopy.

- Anti-DsbA antiserum gave a halo of reacting antibodies around the wild type Nm (8013) which was reduced to the background level of reactivity of the secondary (sheep anti-rabbit immunoglobulin G) antibody alone in the case of the DsbA mutant. These results
- 20 are illustrated by figures 47A and 47B, which show an immunofluorescence microscopy of wild-type and DsbA mutant bacteria with anti-recombinant DsbA antiserum: figure 47A, wild-type Nm 8013 reacted with anti-DsbA antiserum and revealed with anti-rabbit immunoglobulin G-Cy3 conjugate ; figure 47B, DsbA mutant 8013 reacted with anti-DsbA antiserum and revealed with anti-rabbit immunoglobulin G-Cy3 conjugate.

- 25 This demonstrates that the DsbA protein is exposed at the surface of the bacteria.

## V. Assay for the bactericidal activity of the rabbit anti-recombinant DsbA antiserum

Volumes of 10  $\mu$ l of PBS containing 2000 bacteria were mixed with 500  $\mu$ l of freshly-thawed rabbit serum. Volumes of 95  $\mu$ l were taken from the assays for enumeration immediately and at time points up to 90 minutes after addition of the serum. Enumeration was performed by plating 50  $\mu$ l aliquots of 10-fold dilutions of the assays onto GCB agar (Difco).

The results show that while the antiserum killed 65% of the parental meningococcus (strain 8013) within 20 minutes and all of the bacteria within 60 minutes, the preimmune serum (serum taken from the rabbit before the first immunisation) killed none after 20 minutes and only half after 60 minutes. Hence the antiserum is capable of killing heterologous meningococci (The DsbA sequence was taken from strain Z2491). This is illustrated by figure 48 which shows the bactericidal activity of anti-DsbA and the corresponding preimmune antiserum.

The bactericidal activity of the antiserum against the parental strain 8013 was compared with that against the isogenic mutant containing an interrupted DsbA gene (and shown by western blot not to express this protein). In this case freshly-thawed anti-recombinant DsbA antiserum was added to the parental and to the DsbA mutant. The results show that the bactericidal activity is specific for the DsbA-expressing strain, since the parental strain was killed to a much greater extent than was the mutant. This is illustrated by figure 49, which shows the bactericidal activity of anti-DsbA antiserum against meningococci expressing an isogenic mutant lacking the protein DsbA.

SEQUENCE LISTING BRIEF SUMMARY

SEQ ID N°	Sequence nature	Nm strain source	product name	
				<b>DsbA</b>
				<b>Allele 1</b>
1	nucleotides	Z2491	<i>dsbA</i>	
2	aminoacids	Z2491	DsbA	
3	nucleotides	Z3524	<i>dsbA</i>	
4	aminoacids	Z3524	DsbA	
5	nucleotides	Z3842	<i>dsbA</i>	
6	aminoacids	Z3842	DsbA	
7	nucleotides	Z4667	<i>dsbA</i>	
8	aminoacids	Z4667	DsbA	
9	nucleotides	Z4707	<i>dsbA</i>	
10	aminoacids	Z4707	DsbA	
11	nucleotides	Z5005	<i>dsbA</i>	



12	aminoacids	Z5005	DsbA	
13	nucleotides	Z6466	<i>dsbA</i>	
14	aminoacids	Z6466	DsbA	
15	nucleotides	Z7176	<i>dsbA</i>	
16	aminoacids	Z7176	DsbA	
				<b>DsbA</b> <b>Allele 2</b>
17	nucleotides	Z4662	<i>dsbA</i>	
18	aminoacids	Z4662	DsbA	
19	nucleotides	Z6904	<i>dsbA</i>	
20	aminoacids	Z6904	Dsba	
				<b>DsbA</b> <b>Allele 3</b>
21	nucleotides	Z4259	<i>dsbA</i>	
22	aminoacids	Z4259	DsbA	
23	nucleotides	Z4673	<i>dsbA</i>	

24	aminoacids	Z4673	DsbA	DsbA Allele 4
25	nucleotides	Z4683	<i>dsbA</i>	
26	aminoacids	Z4683	DsbA	FhaB
27	nucleotides (3' end 1047 ones)	Z2491	<i>fhaB</i>	
28	aminoacids	Z2491	FhaB	FhuA
29	nucleotides	Z2491	<i>fhuA</i>	
30	aminoacids	Z2491	FhuA	
31	nucleotides	Z3524	<i>fhuA</i>	
32	aminoacids	Z3524	FhuA	
33	nucleotides	Z3842	<i>fhuA</i>	
34	aminoacids	Z3842	FhuA	
35	nucleotides	Z4259	<i>fhuA</i>	
36	aminoacids	Z4259	FhuA	

37	nucleotides	Z4662	<i>fhuA</i>
38	aminoacids	Z4662	FhuA
39	nucleotides	Z4667	<i>fhuA</i>
40	aminoacids	Z4667	FhuA
41	nucleotides	Z4673	<i>fhuA</i>
42	aminoacids	Z4673	FhuA
43	nucleotides	Z4683	<i>fhuA</i>
44	aminoacids	Z4683	FhuA
45	nucleotides	Z4707	<i>fhuA</i>
46	aminoacids	Z4707	FhuA
47	nucleotides	Z5005	<i>fhuA</i>
48	aminoacids	Z5005	FhuA
49	nucleotides	Z6904	<i>fhuA</i>
50	aminoacids	Z6904	FhuA

51	nucleotides	Z7176	<i>fmuA</i>	
52	aminoacids	Z7176	FhuA	
				<b>Rni5</b>
53	nucleotides	Z2491	<i>rni5</i>	
54	aminoacids	Z2491	Rni5	
				<b>Rth17 à 21</b>
55	nucleotides	Z2491	<i>Rth17</i>	
56	aminoacids	Z2491	Rth17	
57	nucleotides	Z2491	<i>rth18</i>	
58	aminoacids	Z2491	Rth18	
59	nucleotides	Z2491	<i>rth19</i>	
60	aminoacids	Z2491	Rth19	
61	nucleotides	Z2491	<i>rth20</i>	
62	aminoacids	Z2491	Rth20	
63	nucleotides	Z2491	<i>rth21</i>	
64	aminoacids	Z2491	Rth21	

				<b>TolC</b> <b>Allele 1</b>
65	nucleotides	Z2491	<i>tolC</i>	
66	aminoacids	Z2491	TolC	
67	nucleotides	Z3524	<i>tolC</i>	
68	aminoacids	Z3524	TolC	
				<b>TolC</b> <b>Allele 2</b>
69	nucleotides	Z4707	<i>tolC</i>	
70	aminoacids	Z4707	TolC	
				<b>TolC</b> <b>Allele 3</b>
71	nucleotides	Z3842	<i>tolC</i>	
72	aminoacids	Z3842	TolC	
73	nucleotides	Z4259	<i>tolC</i>	
74	aminoacids	Z4259	TolC	
75	nucleotides	Z4662	<i>tolC</i>	

76	aminoacids	Z4662	TolC
77	nucleotides	Z4667	<i>tolC</i>
78	aminoacids	Z4667	TolC
79	nucleotides	Z4673	<i>tolC</i>
80	aminoacids	Z4673	TolC
81	nucleotides	Z4683	<i>tolC</i>
82	aminoacids	Z4683	TolC
83	nucleotides	Z5005	<i>tolC</i>
84	aminoacids	Z5005	TolC
85	nucleotides	Z6466	<i>tolC</i>
86	aminoacids	Z6466	TolC
87	nucleotides	Z6904	<i>tolC</i>
88	aminoacids	Z6904	TolC
89	nucleotides	Z7176	<i>tolC</i>
90	aminoacids	Z7176	TolC

				PCR oligo
91	nucleotidic forward primer	Z2491	<i>dsbA</i> 5' end	<i>dsbA</i>
92	nucleotidic reverse primer	Z2491	<i>dsbA</i> 5' end	

93	nucleotidic forward primer	Z2491	<i>dsbA</i> 3' end	
94	nucleotidic reverse primer	Z2491	<i>dsbA</i> 3' end	
95	nucleotidic forward primer	Z2491	<i>dsbA</i> 5' end	
96	nucleotidic reverse primer	Z2491	<i>dsbA</i> 3' end	
				<b>Primers</b>
97	nucleotidic forward primer	Z2491	<i>dsbA</i>	<i>dsbA</i>
98	nucleotidic reverse primer	Z2491	<i>dsbA</i>	
99	nucleotidic forward primer	Z2491	<i>fhuA</i>	<i>fhuA</i>
100	nucleotidic reverse primer	Z2491	<i>fhuA</i>	
101	nucleotidic forward primer	Z2491	<i>rni5</i>	<i>rni5</i>
102	nucleotidic reverse primer	Z2491	<i>rni5</i>	
103	nucleotidic forward primer	Z2491	<i>tolC</i>	<i>tolC</i>
104	nucleotidic reverse primer	Z2491	<i>tolC</i>	
105	nucleotidic forward primer	Z2491	<i>rth17</i>	<i>rth17</i>
106	nucleotidic	Z2491	<i>rth17</i>	



	reverse primer			
107	nucleotidic forward primer	Z2491	<i>rth18</i>	<i>rth18</i>
108	nucleotidic reverse primer	Z2491	<i>rth18</i>	
109	nucleotidic forward primer	Z2491	<i>rth19</i>	<i>rth19</i>
110	nucleotidic reverse primer	Z2491	<i>rth19</i>	
111	nucleotidic forward primer	Z2491	<i>rth20</i>	<i>rth20</i>
112	nucleotidic reverse primer	Z2491	<i>rth20</i>	
113	nucleotidic forward primer	Z2491	<i>rth21</i>	<i>rth21</i>
114	nucleotidic reverse primer	Z2491	<i>rth21</i>	
115	nucleotidic forward primer	Z2491	<i>fhaB</i>	<i>fhaB</i>
116	nucleotidic reverse primer	Z2491	<i>fhaB</i>	

**CLAIMS:**

1. An isolated polypeptide comprising an amino acid sequence which has at least 70% identity to the amino acid sequence selected from the group consisting of: SEQ ID NO:2, SEQ ID NO : 4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO : 10, SEQ ID NO : 12, SEQ ID NO : 14, SEQ ID NO : 16, SEQ ID NO : 18, SEQ ID NO : 20, SEQ ID NO : 22, SEQ ID NO : 24, SEQ ID NO : 26, SEQ ID NO : 28, SEQ ID NO : 30, SEQ ID NO : 32, SEQ ID NO : 34, SEQ ID NO : 36, SEQ ID NO : 38, SEQ ID NO : 40, SEQ ID NO : 42, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID NO : 48, SEQ ID NO : 50, SEQ ID NO : 52, SEQ ID NO : 54, SEQ ID NO : 56, SEQ ID NO : 58, SEQ ID NO : 60, SEQ ID NO : 62, SEQ ID NO : 64, SEQ ID NO : 66, SEQ ID NO : 68, SEQ ID NO : 70, SEQ ID NO : 72, SEQ ID NO : 74, SEQ ID NO : 76, SEQ ID NO : 78, SEQ ID NO : 80, SEQ ID NO : 82, SEQ ID NO : 84, SEQ ID NO : 86, SEQ ID NO : 88, SEQ ID NO : 90.

15

2. An isolated polypeptide as claimed in claim 1 in which the amino acid sequence has at least 95% identity to the amino acid sequence selected from the group consisting of: SEQ ID NO:2, SEQ ID NO : 4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO : 10, SEQ ID NO : 12, SEQ ID NO : 14, SEQ ID NO : 16, SEQ ID NO : 18, SEQ ID NO : 20, SEQ ID NO : 22, SEQ ID NO : 24, SEQ ID NO : 26, SEQ ID NO : 28, SEQ ID NO : 30, SEQ ID NO : 32, SEQ ID NO : 34, SEQ ID NO : 36, SEQ ID NO : 38, SEQ ID NO : 40, SEQ ID NO : 42, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID NO : 48, SEQ ID NO : 50, SEQ ID NO : 52, SEQ ID NO : 54, SEQ ID NO : 56, SEQ ID NO : 58, SEQ ID NO : 60, SEQ ID NO : 62, SEQ ID NO : 64, SEQ ID NO : 66, SEQ ID NO : 68, SEQ ID NO : 70, SEQ ID NO : 72, SEQ ID NO : 74, SEQ ID NO : 76, SEQ ID NO : 78, SEQ ID NO : 80, SEQ ID NO : 82, SEQ ID NO : 84, SEQ ID NO : 86, SEQ ID NO : 88, SEQ ID NO : 90.

25

3. The polypeptide as claimed in claim 1 comprising the amino acid sequence selected from the group consisting of: SEQ ID NO:2, SEQ ID NO : 4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO : 10, SEQ ID NO : 12, SEQ ID NO : 14, SEQ ID NO : 16, SEQ ID NO : 18, SEQ ID NO : 20, SEQ ID NO : 22, SEQ ID NO : 24, SEQ ID NO : 26, SEQ ID NO : 28, SEQ ID NO : 30, SEQ ID NO : 32, SEQ ID NO : 34, SEQ ID NO : 36, SEQ ID NO : 38, SEQ ID NO : 40, SEQ ID NO : 42, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID NO : 48, SEQ ID NO : 50, SEQ ID NO : 52, SEQ ID NO : 54, SEQ ID NO : 56, SEQ ID NO : 58, SEQ ID NO : 60, SEQ ID NO : 62, SEQ ID NO : 64, SEQ ID NO : 66, SEQ ID NO : 68, SEQ ID NO : 70, SEQ ID NO : 72, SEQ ID NO : 74, SEQ ID NO : 76, SEQ ID NO : 78, SEQ ID NO : 80, SEQ ID NO : 82, SEQ ID NO : 84, SEQ ID NO : 86, SEQ ID NO : 88, SEQ ID NO : 90.

30

NO : 38, SEQ ID NO : 40, SEQ ID NO : 42, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID  
NO : 48, SEQ ID NO : 50, SEQ ID NO : 52, SEQ ID NO : 54, SEQ ID NO : 56, SEQ ID  
NO : 58, SEQ ID NO : 60, SEQ ID NO : 62, SEQ ID NO : 64, SEQ ID NO : 66, SEQ ID  
NO : 68, SEQ ID NO : 70, SEQ ID NO : 72, SEQ ID NO : 74, SEQ ID NO : 76, SEQ ID  
5 NO : 78, SEQ ID NO : 80, SEQ ID NO : 82, SEQ ID NO : 84, SEQ ID NO : 86, SEQ ID  
NO : 88, SEQ ID NO : 90.

4. An isolated polypeptide of SEQ ID NO:2, SEQ ID NO : 4, SEQ ID NO:6, SEQ ID  
NO:8, SEQ ID NO : 10, SEQ ID NO : 12, SEQ ID NO : 14, SEQ ID NO : 16, SEQ ID  
10 NO : 18, SEQ ID NO : 20, SEQ ID NO : 22, SEQ ID NO : 24, SEQ ID NO : 26, SEQ ID  
NO : 28, SEQ ID NO : 30, SEQ ID NO : 32, SEQ ID NO : 34, SEQ ID NO : 36, SEQ ID  
NO : 38, SEQ ID NO : 40, SEQ ID NO : 42, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID  
NO : 48, SEQ ID NO : 50, SEQ ID NO : 52, SEQ ID NO : 54, SEQ ID NO : 56, SEQ ID  
NO : 58, SEQ ID NO : 60, SEQ ID NO : 62, SEQ ID NO : 64, SEQ ID NO : 66, SEQ ID  
15 NO : 68, SEQ ID NO : 70, SEQ ID NO : 72, SEQ ID NO : 74, SEQ ID NO : 76, SEQ ID  
NO : 78, SEQ ID NO : 80, SEQ ID NO : 82, SEQ ID NO : 84, SEQ ID NO : 86, SEQ ID  
NO : 88, SEQ ID NO : 90.

5. An immunogenic fragment of the polypeptide as claimed in any one of claims 1 to 4 in  
20 which the immunogenic activity of said immunogenic fragment is substantially the same  
as the polypeptide of SEQ ID NO:2, SEQ ID NO : 4, SEQ ID NO:6, SEQ ID NO:8, SEQ  
ID NO : 10, SEQ ID NO : 12, SEQ ID NO : 14, SEQ ID NO : 16, SEQ ID NO : 18, SEQ  
ID NO : 20, SEQ ID NO : 22, SEQ ID NO : 24, SEQ ID NO : 26, SEQ ID NO : 28, SEQ  
ID NO : 30, SEQ ID NO : 32, SEQ ID NO : 34, SEQ ID NO : 36, SEQ ID NO : 38, SEQ  
25 ID NO : 40, SEQ ID NO : 42, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID NO : 48, SEQ  
ID NO : 50, SEQ ID NO : 52, SEQ ID NO : 54, SEQ ID NO : 56, SEQ ID NO : 58, SEQ  
ID NO : 60, SEQ ID NO : 62, SEQ ID NO : 64, SEQ ID NO : 66, SEQ ID NO : 68, SEQ  
ID NO : 70, SEQ ID NO : 72, SEQ ID NO : 74, SEQ ID NO : 76, SEQ ID NO : 78, SEQ  
ID NO : 80, SEQ ID NO : 82, SEQ ID NO : 84, SEQ ID NO : 86, SEQ ID NO : 88, SEQ  
30 ID NO : 90.

6. An isolated polynucleotide comprising a nucleotide sequence encoding a polypeptide that

has at least 70% identity to the amino acid sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, or 100 over the entire length of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90 respectively; or a nucleotide sequence complementary to said isolated polynucleotide.

7. An isolated polynucleotide comprising a nucleotide sequence that has at least 70% identity to a nucleotide sequence encoding a polypeptide of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, or 90 over the entire coding region; or a nucleotide sequence complementary to said isolated polynucleotide.

8. An isolated polynucleotide which comprises a nucleotide sequence which has at least 70% identity to that of SEQ ID NO : 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89 over the entire length of SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89 respectively; or a nucleotide sequence complementary to said isolated polynucleotide.

9. The isolated polynucleotide as claimed in any one of claims 6 to 8 in which the identity is at least 95% to SEQ ID NO : 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, or 89.

10. An isolated polynucleotide comprising a nucleotide sequence encoding the polypeptide of SEQ ID NO:2, SEQ ID NO : 4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO : 10, SEQ

ID NO : 12, SEQ ID NO : 14, SEQ ID NO : 16, SEQ ID NO : 18, SEQ ID NO : 20, SEQ  
ID NO : 22, SEQ ID NO : 24, SEQ ID NO : 26, SEQ ID NO : 28, SEQ ID NO : 30, SEQ  
ID NO : 32, SEQ ID NO : 34, SEQ ID NO : 36, SEQ ID NO : 38, SEQ ID NO : 40, SEQ  
ID NO : 42, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID NO : 48, SEQ ID NO : 50, SEQ  
5 ID NO : 52, SEQ ID NO : 54, SEQ ID NO : 56, SEQ ID NO : 58, SEQ ID NO : 60, SEQ  
ID NO : 62, SEQ ID NO : 64, SEQ ID NO : 66, SEQ ID NO : 68, SEQ ID NO : 70, SEQ  
ID NO : 72, SEQ ID NO : 74, SEQ ID NO : 76, SEQ ID NO : 78, SEQ ID NO : 80, SEQ  
ID NO : 82, SEQ ID NO : 84, SEQ ID NO : 86, SEQ ID NO : 88, SEQ ID NO : 90.

10 11. An isolated polynucleotide comprising the polynucleotide of SEQ ID NO : 1, SEQ ID  
NO : 3, SEQ ID NO : 5, SEQ ID NO : 7, SEQ ID NO : 9, SEQ ID NO : 11, SEQ ID NO :  
13, SEQ ID NO : 15, SEQ ID NO : 17, SEQ ID NO : 19, SEQ ID NO : 21, SEQ ID NO :  
23, SEQ ID NO : 25, SEQ ID NO : 27, SEQ ID NO : 29, SEQ ID NO : 31, SEQ ID NO :  
33, SEQ ID NO : 35, SEQ ID NO : 37, SEQ ID NO : 39, SEQ ID NO : 41, SEQ ID NO :  
15 43, SEQ ID NO : 45, SEQ ID NO : 47, SEQ ID NO : 49, SEQ ID NO : 51, SEQ ID NO :  
53, SEQ ID NO : 55, SEQ ID NO : 57, SEQ ID NO : 59, SEQ ID NO : 61, SEQ ID NO :  
63, SEQ ID NO : 65, SEQ ID NO : 67, SEQ ID NO : 69, SEQ ID NO : 71, SEQ ID NO :  
73, SEQ ID NO : 75, SEQ ID NO : 77, SEQ ID NO : 79, SEQ ID NO : 81, SEQ ID NO :  
83, SEQ ID NO : 85, SEQ ID NO : 87, SEQ ID NO : 89.

20

12. An isolated polynucleotide comprising a nucleotide sequence encoding the polypeptide  
of SEQ ID NO:2, SEQ ID NO : 4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO : 10, SEQ  
ID NO : 12, SEQ ID NO : 14, SEQ ID NO : 16, SEQ ID NO : 18, SEQ ID NO : 20, SEQ  
ID NO : 22, SEQ ID NO : 24, SEQ ID NO : 26, SEQ ID NO : 28, SEQ ID NO : 30, SEQ  
ID NO : 32, SEQ ID NO : 34, SEQ ID NO : 36, SEQ ID NO : 38, SEQ ID NO : 40, SEQ  
25 ID NO : 42, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID NO : 48, SEQ ID NO : 50, SEQ  
ID NO : 52, SEQ ID NO : 54, SEQ ID NO : 56, SEQ ID NO : 58, SEQ ID NO : 60, SEQ  
ID NO : 62, SEQ ID NO : 64, SEQ ID NO : 66, SEQ ID NO : 68, SEQ ID NO : 70, SEQ  
ID NO : 72, SEQ ID NO : 74, SEQ ID NO : 76, SEQ ID NO : 78, SEQ ID NO : 80, SEQ

ID NO : 82, SEQ ID NO : 84, SEQ ID NO : 86, SEQ ID NO : 88, or SEQ ID NO : 90, obtainable by screening an appropriate library under stringent hybridization conditions with a labeled probe having the sequence of SEQ ID NO : 1, SEQ ID NO : 3, SEQ ID NO : 5, SEQ ID NO : 7, SEQ ID NO : 9, SEQ ID NO : 11, SEQ ID NO : 13, SEQ ID NO : 15, SEQ ID NO : 17, SEQ ID NO : 19, SEQ ID NO : 21, SEQ ID NO : 23, SEQ ID NO : 25, SEQ ID NO : 27, SEQ ID NO : 29, SEQ ID NO : 31, SEQ ID NO : 33, SEQ ID NO : 35, SEQ ID NO : 37, SEQ ID NO : 39, SEQ ID NO : 41, SEQ ID NO : 43, SEQ ID NO : 45, SEQ ID NO : 47, SEQ ID NO : 49, SEQ ID NO : 51, SEQ ID NO : 53, SEQ ID NO : 55, SEQ ID NO : 57, SEQ ID NO : 59, SEQ ID NO : 61, SEQ ID NO : 63, SEQ ID NO : 65, SEQ ID NO : 67, SEQ ID NO : 69, SEQ ID NO : 71, SEQ ID NO : 73, SEQ ID NO : 75, SEQ ID NO : 77, SEQ ID NO : 79, SEQ ID NO : 81, SEQ ID NO : 83, SEQ ID NO : 85, SEQ ID NO : 87, or SEQ ID NO : 89, or a fragment thereof.

13. An expression vector or a recombinant live microorganism comprising an isolated polynucleotide according to any one of claims 6-12.

14. A host cell comprising the expression vector of claim 13 or a membrane of said host cell expressing an isolated polypeptide comprising an amino acid sequence that has at least 70% identity to the amino acid sequence selected from the group consisting of : SEQ ID NO:2, SEQ ID NO : 4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO : 10, SEQ ID NO : 12, SEQ ID NO : 14, SEQ ID NO : 16, SEQ ID NO : 18, SEQ ID NO : 20, SEQ ID NO : 22, SEQ ID NO : 24, SEQ ID NO : 26, SEQ ID NO : 28, SEQ ID NO : 30, SEQ ID NO : 32, SEQ ID NO : 34, SEQ ID NO : 36, SEQ ID NO : 38, SEQ ID NO : 40, SEQ ID NO : 42, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID NO : 48, SEQ ID NO : 50, SEQ ID NO : 52, SEQ ID NO : 54, SEQ ID NO : 56, SEQ ID NO : 58, SEQ ID NO : 60, SEQ ID NO : 62, SEQ ID NO : 64, SEQ ID NO : 66, SEQ ID NO : 68, SEQ ID NO : 70, SEQ ID NO : 72, SEQ ID NO : 74, SEQ ID NO : 76, SEQ ID NO : 78, SEQ ID NO : 80, SEQ ID NO : 82, SEQ ID NO : 84, SEQ ID NO : 86, SEQ ID NO : 88, or SEQ ID NO : 90.

15. A process for producing a polypeptide comprising an amino acid sequence that has at

least 70% identity to the amino acid sequence selected from the group consisting of:

SEQ ID NO:2, SEQ ID NO : 4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO : 10, SEQ ID NO : 12, SEQ ID NO : 14, SEQ ID NO : 16, SEQ ID NO : 18, SEQ ID NO : 20, SEQ ID NO : 22, SEQ ID NO : 24, SEQ ID NO : 26, SEQ ID NO : 28, SEQ ID NO : 30, SEQ ID NO : 32, SEQ ID NO : 34, SEQ ID NO : 36, SEQ ID NO : 38, SEQ ID NO : 40, SEQ ID NO : 42, SEQ ID NO : 44, SEQ ID NO : 46, SEQ ID NO : 48, SEQ ID NO : 50, SEQ ID NO : 52, SEQ ID NO : 54, SEQ ID NO : 56, SEQ ID NO : 58, SEQ ID NO : 60, SEQ ID NO : 62, SEQ ID NO : 64, SEQ ID NO : 66, SEQ ID NO : 68, SEQ ID NO : 70, SEQ ID NO : 72, SEQ ID NO : 74, SEQ ID NO : 76, SEQ ID NO : 78, SEQ ID NO : 80, SEQ ID NO : 82, SEQ ID NO : 84, SEQ ID NO : 86, SEQ ID NO : 88, or SEQ ID NO : 90 comprising culturing a host cell of claim 18 under conditions sufficient for the production of said polypeptide and recovering the polypeptide from the culture medium.

16. A process for expressing a polynucleotide of any one of claims 6 – 12 comprising transforming a host cell with the expression vector comprising at least one of said polynucleotides and culturing said host cell under conditions sufficient for expression of any one of said polynucleotides.

17. A vaccine composition comprising an effective amount of the polypeptide of any one of claims 1 to 5 and a pharmaceutically acceptable carrier.

18. A vaccine composition comprising an effective amount of the polynucleotide of any one of claims 6 to 12 and a pharmaceutically effective carrier.

19. The vaccine composition according to either one of claims 17 or 18 wherein said composition comprises at least one other *Neisseria meningitidis* antigen.

20. An antibody immunospecific for the polypeptide or immunological fragment as

claimed in any one of claims 1 to 5.

21. A method of diagnosing a *Neisseria* infection, comprising identifying a polypeptide as claimed in any one of claims 1 - 5, or an antibody that is immunospecific for said polypeptide, present within a biological sample from an animal suspected of having such an infection.

22. Use of a composition comprising an immunologically effective amount of a polypeptide as claimed in any one of claims 1 - 5 in the preparation of a medicament for use in generating an immune response in an animal.

23. Use of a composition comprising an immunologically effective amount of a polynucleotide as claimed in any one of claims 6 - 12 in the preparation of a medicament for use in generating an immune response in an animal.

24. A therapeutic composition useful in treating humans with *Neisseria meningitidis* disease comprising at least one antibody directed against the polypeptide of claims 1 - 5 and a suitable pharmaceutical carrier.



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(54) Title: NOVEL *NEISSERIA MENINGITIDIS* COMPOUNDS AND ANTI-INFECTION APPLICATIONS THEREOF

(57) Abstract: The invention provides novel *Neisseria meningitidis* (Nm) polypeptides and polynucleotides which cover the Nm genetic diversity, and which correspond to polypeptide of Nm outer membrane and/or periplasma, and to methods for producing such Nm compounds. Also provided are anti-Nm infection, and particularly diagnostic, prophylactic and therapeutic uses thereof.

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FIGURE 1A

1 ATGAAACTGA AACCTTAGC TTTGACTTCA TTGACCTGT TGGCATTGGC

51 CGCTTGTAGC AACAGGCTG AAACCAGTGT TCCGGCAGAC AGCGCCCAAA

101 GCAGCTCATC TGCTCCGGCA GCCCCTGCTG AGTTGAACGA AGGTGTGAAC

151 TACACTGTAT TGTCTACGCC TATTCCGCAA CAGCAGGCCG GTAAAAATCGA

201 AGTATTGGAA TTTTTCGGCT ACTTCTGCCC GCATTGCGCC CATCTTGAGC

251 CGGTCTTGAG CGAGCACATC AAAACGTTTA AAGACGATAC CTATATGCGC

301 CGGGAGCATG TCGTGTGGGG TGATGAAATG AAACCTTTGG CACGTTTGCC

351 GGCCGCAGTG GAAATGGCCG GTGAATCAGA TAAAGCCAAC AGCCATATTT

401 TCGATGCGAT GGTTAATCAA AAAATCAATC TGGCCGATAC CGATACCCTG

451 AAAAAATGGC TGTCCGAGCA AACAGCGTTT GACGGCAAAA AAGTATTGGC

501 TGCATTTGAG GCTCCTGAAA GCCAAGCGCG TCGGCTCAA ATGGAAGAGT

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551 TGACCAATAA ATTCCAAATC AGCGGCACAC CGACTGTGAT TGTCGGCGGC

601 AAATACCAAG TTGAATTAA AGACTGGCAG TCCGGTATGA CCACGATTGA

651 CCAGTTGGTG GATAAAGTAC GCGAAGAGCA GAAAAAGCCG CAATAA

FIGURE 1A (suite)

FIGURE 1B

1 MKLKTALTS LTLLALAACS KQAETSVPAD SAQSSSSAPA APAELNEGVN

51 YTVLSTPIQ QQAGKIEVLE FFGYFCPHCA HLEPVLSEHI KTFKDDTYMR

101 REHVVGDEM KPLARLAAAV EMAGESDKAN SHIFDAMVNQ KINLADDTL

151 KKWLSEQTAF DGKKVLAAFE APESQARAAQ MEELTNKFQI SGTPTVIVGG

201 KYQVEFKDWQ SGMTTIDQLV DKVREEQKKP Q\*

FIGURE 2A

-----

1 ATGAAACTGA AAACCTTAGC TTTGACTTCA TTGACCCTGT TGGCATTGGC

51 CGCTTGTAGC AAACAGGCTG AAACCAAGTGT TCCGGCAGAC AGCGCCCAAA

101 GCAGCTCATC TGCTCCGGCA GCCCCTGCTG AGTTGAACGA AGGTGTGAAC

151 TAACTGTAT TGTCTACGCC TATTCCGCAA CAGCAGGCCG GTAAAATCGA

201 AGTATTGGAA TTTTTCGGCT ACTTCTGCCC GCATTGCGCC CATCTTGAGC

251 CGGTCTTGAG CGAGCACATC AAAACGTTTA AAGACGATAC CTATATGCGC

301 CGGGAGCATG TCGTGTGGGG TGATGAAATG AAACCTTTGG CACGTTTGGC

351 GGCCGCAGTG GAAATGGCCG GTGAATCAGA TAAAGCCAAC AGCCATATTT

401 TCGATGCGAT GGTTAATCAA AAAATCAATC TGGCCGATAC CGATACCCTG

451 AAAAAATGGC TGTCAGAGCA AACAGCGTTT GACGGCAAAA AAGTATTGGC

501 TGCATTTGAG GTCCTGAAA GCCAAGCGCG TCGGCTCAA ATGGAAGAGT

551 TGACCAATAA ATTCCAAATC AGCGGCACAC CGACTGTGAT TGTCGGCGGC

601 AAATACCAAG TTGAATTTAA AGACTGGCAG TCCGGTATGA CCACGATTGA

651 CCAGTTGGTG GATAAAGTAC GCGAAGAGCA GAAAAAGCCG CAATAA

FIGURE 2A (suite)

FIGURE 2B

1 MKLKTALTS LTLLALAACS KQAETSVPAD SAQSSSSAPA APAELNEGVN  
51 YTVLSTPIQ QQAGKIEVLE FFGYFCPHCA HLEPVLSEHI KTFKDDTYMR  
101 REHVVGDEM KPLARLAAAV EMAGESDKAN SHIFDAMVNQ KINLADTDTL  
151 KKWLSEQTAF DGKKVLAAFE APESQARAAQ MEELTNKFQI SGTPTVIVGG  
201 KYQVEFKDWQ SGMTTIDQLV DKVREEQKKP Q\*

## FIGURE 1A

1 ATGAAACTGA AAACCTTAGC TTTGACTTCA TTGACCCTGT TGGCATTGGC

51 CGCTTGTAGC AAACAGGCTG AAACCAGTGT TCCGGCAGAC AGCGCCCAAA

101 GCAGCTCATC TGCTCCGGCA GCCCCTGCTG AGTTGAACGA AGGTGTGAAC

151 TACACTGTAT TGTCTACGCC TATTCCGCAA CAGCAGGCCG GTAAAATCGA

201 AGTATTGGAA TTTTTCGGCT ACTTCTGCCC GCATTGCGCC CATCTTGAGC

251 CGGTCTTGAG CGAGCACATC AAAACGTTTA AAGACGATAC CTATATGCGC

301 CGGGAGCATG TCGTGTGGGG TGATGAAATG AAACCTTTGG CACGTTTGGC

351 GGCCGCAGTG GAAATGCGCG GTGAATCAGA TAAAGCCAAC AGCCATATT

401 TCGATGCGAT GGTAAATCAA AAAATCAATC TCGCCGATAC CGATACCCTG

451 AAAAAATGGC TGTCGAGCA AACAGCGTTT GACGGCAAAA AAGTATTGGC

501 TGCATTTGAG GCTCCTGAAA GCCAAGCGCG TCGGCTCAA ATGGAAGAGT



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551 TGACCAATAA ATTCCAAATC AGCGGCACAC CGACTGTGAT TGTGGGCGGC

501 AAATACCAAG TTGAATTAA AGACTGGCAG TCCGGTATGA CCACGATTGA

651 CCAGTTGGTG GATAAAGTAC GCGAAGAGCA GAAAAAGCCG CAATAA

FIGURE 3A (suite)

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FIGURE 3B

1 MKLKTALTS LTLLALAACS KQAETSVPAD SAQSSSSAPA APAELNEGVN

51 YTVLSTPIQ QQAGKIEVLE FFGYFCPHCA HLEPVLSEHI KTFKDDTYMR

101 REHVVGDEM KPLARLAAAV EMAGESDKAN SHIFDAMVNO KINLADDTL

151 KKWLSEQTAF DGKKVLAAFE APESQARAAQ MEELTNKFQI SGTPTVIVGG

201 KYQVEFKDWQ SGMTTIDQLV DKVREEQKKP Q\*

FIGURE 4A

1 ATGAAACTGA AAACCTTAGC TTTGACTTCA TTGACCCTGT TGGCATTGGC

51 CGCTTGTAGC AAACAGGCTG AAACCACTGT TCCGGCAGAC AGCGCCCAAA

101 GCAGCTCATC TGCTCCGGCA GCCCCTGCTG AGTTGAACGA AGGTGTGAAC

151 TAACTGTAT TGTCTACGCC TATTCCGCAA CAGCAGGCCG GTAAAAATCGA

201 AGTATTGGAA TTTTTCGGCT ACTTCTGCCC GCATTGCGCC CATCTTGAGC

251 CGGTCTTGAG CGAGCACATC AAAACGTTTA AAGACGATAC CTATATGCGC

301 CGGGAGCATG TCGTGTGGGG TGATGAAATG AAACCTTTGG CACGTTTGGC

351 GGCCGCAGTG GAAATG<sup>6</sup>CCG GTGAATCAGA TAAAGCCAAC AGCCATATTT

401 TCGATGCGAT GGTTAATCAA AAAATCAATC TGGCCGATAC CGATACCCTG

451 AAAAAATGGC TGTCCGAGCA AACAGCGTTT GACGGCAAAA AAGTATTGGC

501 TGCATTTGAG GCTCCTGAAA GCCAAGCGCG TCGGCTCAA ATGGAAGAGT

551 TGACCAATAA ATTCCAAATC AGCGGCACAC CGACTGTGAT TGTCGGCGGC

601 AAATACCAAG TTGAATTTAA AGACTGGCAG TCCGGTATGA CCACGATTGA

651 CCAGTTGGTG GATAAAGTAC GCGAAGAGCA GAAAAAGCCG CAATAA

FIGURE 4A (suite)

FIGURE 48

1 MKLKTALTS LTLLALAACS KQAETSVPAD SAQSSSSAPA APAELNEGVN

51 YTVLSTPIPQ QQAGKIEVLE FFGYFCPHCA HLEPVLSEHI KTFKDDTYMR

101 REHVVGDEM KPLARLAAAV EMAGESDKAN SHIFDAMVNQ KINLADTDTL

151 KKWLSEQTAF DGKKVLAAFE APESQARAAQ MEELTNKFQI SGTPTVIVGG

201 KYQVEFKDWQ SGMTTIDQLV DKVREEQKKP Q\*

FIGURE 5A

1 ATGAAACTGA AAACCTTAGC TTTGACTTCA TTGACCCTGT TGGCATTGGC  
51 CGCTTGTAGC AAACAGGCTG AAACCAAGTGT TCCGGCAGAC AGCGCCCAAA  
101 GCAGCTCATC TGCTCCGGCA GCCCCTGCTG AGTTGAACGA AGGTGTGAAC  
151 TACACTGTAT TGTCTACGCC TATTCCGCAA CAGCAGGCCG GTAAAATCGA  
201 AGTATTGGAA TTTTTCGGCT ACTTCTGCCC GCATTGCGCC CATCTTGAGC  
251 CGGTCTTGAG CGAGCACATC AAAACGTTTA AAGACGATAC CTATATGCGC  
301 CGGGAGCATG TCGTGTGGGG TGATGAAATG AAACCTTTGG CACGTTTGGC  
351 GGCCGCACTG GAAATGGCCG GTGAATCAGA TAAAGCCAAC AGCCATATTT  
401 TCGATGCGAT GTTAATCAA AAAATCAATC TGGCCGATAC CGATACCCTG  
451 AAAAAATGGC TGCCGAGCA AACAGCGTTT GACGGCAAAA AAGTATTGGC  
501 TGCATTTGAG GCTCCTGAAA GCCAAGCGCG TGCGGCTCAA ATGGAAGAGT

551 TGACCAATAA ATTCCAAATC AGCGGCACAC CGACTGTGAT TGTCGGCGGC

601 AAATACCAAG TTGAATTTAA AGACTGGCAG TCCGGTATGA CCACGATTGA

651 CCAGTTGGTG GATAAAGTAC GCGAAGAGCA GAAAAAGCCG CAATAA

FIGURE 5A (suite)

FIGURE 5B

1 MKLKLTLALTS LTLLALAACS KQAETSVPAD SAQSSSSAPA APAELNEGVN

51 YTVLSTPIQ QQAGKIEVLE FFGYFCPHCA HLEPVLSEHI KTFKDDTYMR

101 REHVVGDEM KPLARLAAAV EMAGESDKAN SHIFDAMVNQ KINLADTDTL

151 KKWLSEQTAF DGKKVLAAFE APESQARAAQ MEELTNKFQI SGTPTVIVGG

201 KYQVEFKDWQ SGMTTIDQLV DKVREEQKKP Q\*



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FIGURE 6A

1 ATGAAACTGA AAACCTTAGC TTTGACTTCA TTGACCTGT TGGCATTGGC

51 CGCTTGTAGC AAACAGGCTG AAACCAGTGT TCCGGCAGAC AGCGCCCAAA

101 GCAGCTCATC TGCTCCGGCA GCCCCTGCTG AGTTGAACGA AGGTGTGAAC

151 TACACTGTAT TGTCTACGCC TATTCCGCAA CAGCAGGCCG GTAAAATCGA

201 AGTATTGGAA TTTTTCGGCT ACTTCTGCCC GCATTGCGCC CATCTTGAGC

251 CGGTCTTGAG CGAGCACATC AAAACGTTTA AAGACGATAC CTATATGCGC

301 CGGGAGCATG TCGTGTGGGG TGATGAAATG AAACCTTTGG CACGTTTGGC

351 GGCCGCAGTG GAAATGGCCG GTGAATCAGA TAAAGCCAAC AGCCATATTT

401 TCGATGCGAT GGTTAATCAA AAAATCAATC TGGCCGATAC CGATACCTGT

451 AAAAAATGGC TGTCCGAGCA AACAGCGTTT GACGCACAAA AAGTATTGGC

501 TGCATTTGAG GCTCCTGAAA GCCAAGCGCG TGCGGCTCAA ATGGAAGAGT

551 TGACCAATAA ATTCCAAATC AGCGGCACAC CGACTGTGAT TGTCGGCGGC

601 AAATACCAAG TTGAATTTAA AGACTGGCAG TCCGGTATGA CCACGATTGA

651 CCAGTTGGTG GATAAAGTAC GCGAAGAGCA GAAAAAGCCG CAATAA

FIGURE 6A (suite)

FIGURE 6B

1 MKLKTALTS LTLLALAACS KQAETSVPAD SAQSSSSAPA APAELNEGVN  
51 YTVLSTPIQ QQAGKIEVLE FFGYFCPHCA HLEPVLSEHI KTFKDDTYMR  
101 REHVVGWDEM KPLARLAAAV EMAGESDKAN SHIFDAMVNQ KINLADDTL  
151 KKWLSEQTAF DGKKVLAAFE APESQARAAQ MEELTNKFQI SGTPTVIVGG  
201 KYQVEFKDWQ SGMTTIDQLV DKVREEQKKP Q\*

FIGURE 7A

1 ATGAACTGA AAACCTTAGC TTTGACTTCA TTGACCCTGT TGGCATTGGC  
51 CGCTTGTAGC AAACAGGCTG AAACCAGTGT TCCGGCAGAC AGCGCCCAAA  
101 GCAGCTCATC TGCTCCGGCA GCCCCTGCTG AGTTGAACGA AGGTGTGAAC  
151 TACACTGTAT TGTCTACGCC TATTCCGCAA CAGCAGGCCG GTAAAAATCGA  
201 AGTATTGGAA TTTTTCGGCT ACTTCTGCCC GCATTGCGCC CATCTTGAGC  
251 CGGTCTTGAG CGAGCACATC AAAACGTTTA AAGACGATAC CTATATGCGC  
301 CGGGAGCATG TCGTGTGGGG TGATGAAATG AAACCTTTGG CACGTTTGGC  
351 GGCCGCAGTG GAAATGGCCG GTGAATCAGA TAAAGCCAAC AGCCATATT  
401 TCGATGCGAT GGTTAATCAA AAAATCAATC TGGCCGATAC CGATACCCTG  
451 AAAAAATGGC TGTCGAGCA AACAGCGTTT GACGGCAAAA AAGTATTGGC  
501 TGCATTTGAG GCTCCTGAAA GCCAAGCGCG TCGGGCTCAA ATGGAAGAGT

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551 TGACCAATAA ATTCCAAATC AGCGGCACAC CGACTGTGAT TGTCGGCGGC

601 AAATACCAAG TTGAATTTAA AGACTGGCAG TCCGGTATGA CCACGATTGA

651 CCAGTTGGTG GATAAAGTAC GCGAAGAGCA GAAAAAGCCG CAATAA

FIGURE 7A (suite)

FIGURE 7B

1 MKLKTALTS LTLLALAACS KQAETSVPAD SAQSSSSAPA APAELNEGVN  
51 YTVLSTPIPQ QQAGKIEVLE FFGYFCPHCA HLEPVLSEHI KTFKDDTYMR  
101 REHV VWGDEM KPLARLAAAV EMAGESDKAN SHIFDAMVNQ KINLADTDTL  
151 KKWLSEQTAF DGKKVLAAFE APESQARAAQ MEELTNKFQ! SGTPTVIVGG  
201 KYQVEFKDWQ SGMTTIDQLV DKVREEQKKP Q\*

FIGURE 8a

1 ATGAACTGA AACCTTAGC TTTGACTTCA TTGACCCTGT TGGCATTGGC  
CGCTTGTAGC AACAGGCTG AAACCAGTGT TCCGGCAGAC AGCGCCCAAA  
101 GCAGTCATC TGCTCCGGCA GCCCCTGCTG AGTTGAACGA AGGTGTGAAC  
151 TACACTGTAT TGTCTACGCC TATTCCGCAA CAGCAGGCCG GTAAAAATCGA  
201 AGTATTGGAA TTTTTCGGCT ACTTCTGCCC GCATTGCGCC CATCTTGAGC  
251 CGGTCTTGAG CGAGCACATC AAAACGTTTA AAGACGATAC CTATATGCGC  
301 CGGGAGCATG TCGTGTGGGG TGATGAAATG AAACCTTTGG CACGTTTGGC  
351 GGCCGCAGTG GAAATG<sup>6</sup>CCG GTGAATCAGA TAAAGCCAAC AGCCATATTT  
401 TCGATGCGAT GGTTAATCAA AAAATCAATC TGGCCGATAC CGATACCCTG  
451 AAAAAATGGC TGTCCGAGCA AACAGCGTTT GACGGCAAAA AAGTATTGGC  
501 TGCATTTGAG GCTCCTGAAA GCCAAGCGCG TGCGGCTCAA ATGGAAGAGT

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551 TGACCAATAA ATTCCAAATC AGCGGCACAC CGACTGTGAT TGTCGGCGGC

601 AAATACCAAG TTGAATTTAA AGACTGGCAG TCCGGTATGA CCACGATTGA

651 CCAGTTGGTG GATAAAGTAC GCGAAGAGCA GAAAAAGCCG CAATAA

FIGURE 8A (suite)



FIGURE 8B

1 MKLKTALTS LTLLALAACS KQAETSVPAD SAQSSSSAPA APAELNEGVN

51 YTVLSTPIPQ QQAGKIEVLE FFGYFCPHCA HLEPVLSEHI KTFKDDTYMR

101 REHVWVGDEM KPLARLAAAV EMAGESDKAN SHIFDAMVNQ KINLADDTL

151 KKWLSEQTAF DGKKVLAAFE APESQARAAQ MEELTNKFQI SGTPTVIVGG

201 KYQVEFKDWQ SGMTTIDQLV DKVREEQKKP Q\*

FIGURE 9a

1 ATGAAACTGA AAACCTTAGC TTGACTTCA TTGACCCTGT TGGCATTGGC  
51 CGCTTGTAGC AAACAGGCTG AAACCAGTGT TCCGGCAGAC AGCGCCCAAA  
101 GCAGCTCATC TGCTCCGGCA GCCCCTGCTG AGTTGAACGA AGGTGTGAAC  
151 TACACTGTAT TGTCTACGCC TATTCCGCAA CAGCAGGCCG GTAAAATCGA  
201 AGTATTGGAA TTTTTCGGCT ACTTCTGCCC GCATTGCGCC CATCTTGAGC  
251 CGGTCTTGAG CGAGCACATC AAAACGTTTA AAGACGATAC CTATATGCGC  
301 CGGGAGCATG TCGTGTGGGG TGATGAAATG AAACCTTTGG CACGTTTGGC  
351 GGCCGCAGTG GAAATGGCCG GTGAATCAGA TAAAGCCAAC AGCCATATTT  
401 TCGATGCGAT GGTTAATCAA AAAATCAATC TGGCCGATAC CGATACCCTG  
451 AAAAAATGGC TGTCCGAGCA AACAGCGTTT GACGGCAAAA AAGTATTGGC  
501 TGCATTTGAG GCTCCTGAAA GCCAAGCGCG TCGGCTCAA ATGGAAGAGT

551 TGACCAATAA ATTCCAAATC AGCGGCACAC CGACTGTGAT TGTCGGCGGC

601 AAATACCAAG TTGAATTTAA AGACTGGCAG TCTGGTATGA CCACGATTGA

651 CCAGTTGGTG GATAAAGTAC GCGAAGAGCA GAAAAAGCCG CAATAA

FIGURE 9A (suite)

FIGURE 9B

1 MKLKLTLALT'S LTLLALAACS KQAETSVPAD SAQSSSSAPA APAELNEGVN

51 YTVLSTPIQ QQAGKIEVLE FFGYFCPHCA HLEPVLSEHI KTFKDDTYMR

101 REHVVGDEM KPLARLAAAV EMAGESDKAN SHIFDAMVNQ KINLADTDTL

151 KKWLSEQTAF DGKKVLAAFE APESQARAAQ MEELTNKFQI SGTPTVIVGG

201 KYQVEFKDWQ SGMTTIDQLV DKVREEQKKP Q\*

FIGURE 10A

1 ATGAAACTGA AACCTTAGC TTGACTTCA TTGACCCTGT TGGCATTGGC

51 CGCTTGTAGC AAACAGGCTG AAACCAAGTGT TCCGGCAGAC AGCGCCCAAA

101 GCAGCTCATC TGCTCCGGCA GCCCCTGCTG AGTTGAACGA AGGTGTGAAC

151 TAACTGTAT TGTCTACGCC TATTCCGCAA CAGCAGGCCG GTAAAAATCGA

201 AGTATTGGAA TTTTTCGGCT ACTTCTGCCC GCATTGCGCC CATCTTGAGC

251 CGGTCTTGAG CGAGCACATC AAAACGTTTA AAGACGATAC CTATATGCGC

301 CGGGAGCATG TCGTGTGGGG TGATGAAATG AAACCTTTGG CACGTTTGGC

351 GGCCGCAGTG GAAATG<sup>6</sup>CCG GTGAATCAGA TAAAGCCAAC AGCCATATT

401 TCGATGCGAT GGTTAATCAA AAAATCAATC TGGCCGATAC CGATACCCCTG

451 AAAAAATGGC TGTCGAGCA AACAGCGTTT GACGGCAAAA AAGTATTGGC

501 TGCATTTGAG GCTCCTGAAA GCCAAGCGCG TCGGCTCAA ATGGAAGAGT

551 TGACCAATAA ATTCCAAATC AGCGGCACAC CGACTGTGAT TGTCGGCGGC

601 AAATACCAAG TTGAATTTAA AGACTGGCAG TCTGGTATGA CCACGATTGA

651 CCAGTTGGTG GATAAAGTAC GCGAAGAGCA GAAAAAGCCG CAATAA

FIGURE 10A (suite)

FIGURE 103

1 MKLKTALTS LTLLALAACS KQAETSVPAD SAQSSSSAPA APAELNEGVN

51 YTVLSTPIPQ QQAGKIEVLE FFGYFCPHCA HLEPVLSEHI KTFKDDTYMR

101 REHVVGDEM KPLARLAAAV EMAGESDKAN SHIFDAMVNQ KINLADTDTL

151 KKWLSEQTAF DGKKVLAAFE APESQARAAQ MEELTNKFQI SGTPTVIVGG

201 KYQVEFKDWQ SGMTTIDQLV DKVREEQKKP Q\*

FIGURE 11a

1 ATGAAACTGA AAACCTTAGC TTTGACTTCA TTGACCCTGT TGGCATTGGC

51 CGCTTGTAGC AAACAGGCTG AAACCAGCGT TCCGGCAGAC AGCGTCCAAA

101 GCAGCTCATC TGCTCCGGCA GCCCCAGCCC CATTGACCGA AGGCGTGAAC

151 TAACTGTAT TGTCCACGCC TATCCCGCAA CAGCAGGCCG GCAAAGTCGA

201 AGTCTTGAA TTTTTCGGCT ACTTCTGCC GCATTGCGCC CATCTTGAGC

251 CGGTCTTGAG CGAGCACATC AAAACGTTTA AAGACGATAC CTATATGCGC

301 CGGGAGCATG TCGTGTGGGG TGATGAAATG AAACCTTTGG CACGTTTGGC

351 GGCCGCAGTG GAAATGCGCG GTGAATCAGA TAAAGCCAAC AGCCATATTT

401 TCGATGCGAT GGTTAATCAA AAAATCAATC TGGCCGATAC CGATACCCTG

451 AAAAAATGGC TGTCCGAGCA AACAGCGTTT GACGGCAAAA AAGTATTGGC

501 TGCATTTGAG GCTTCTGAAA GCCAAGCGCG TCGGCTCAA ATGGAAGAGT



551 TGACCAATAA ATTCCAAATC AGCGGCACAC CGACTGTGAT CGTCGGCGGC

601 AAATACCAAG TTGAATTTAA AGACTGGCAG TCCGGTATGA CCACGATTGA

651 CCAGTTGGTG GATAAAGTAC GCGAAGAGCA GAAAAAGCCG CAATAA

FIGURE 11A (suite)

FIGURE 115

1 MKLKTALTS LTLLALAACS KQAETSVPAD SVQSSSSAPA APAPLTEGVN  
51 YTVLSTPIQ QQAGKVEVLE FFGYFCPHCA HLEPVLSEHI KTFKDDTYMR  
101 REHVVGDEM KPLARLAAAV EMAGESDKAN SHIFDAMVNQ KINLADTDTL  
151 KKWLSEQTAF DGKKVLAAFE ASESQARAAQ MEELTNKFQI SGTPTVIVGG  
201 KYQVEFKDWQ SGMTTIDQLV DKVREEQKKP Q\*

FIGURE 12A

1 ATGAAACTGA AACCTTAGC TTGACTTCA TTGACCCTGT TGGCATTGGC  
51 CGCTTGTAGC AAACAGGCTG AAACCAGCGT TCCGGCAGAC AGCGTCCAAA  
101 GCAGCTCATC TGCTCCGGCA GCCCCAGCCC CATTGACCGA AGGCGTGAAC  
151 TACACTGTAT TGTCCACGCC TATCCGCAA CAGCAGGCCG GCAAAGTCGA  
201 AGTCTTGAA TTTTTCGGCT ACTTCTGCCC GCATTGCGCC CATCTTGAGC  
251 CGGTCTTGAG CGAGCACATC AAAACGTTTA AAGACGATAC CTATATGCGC  
301 CGGGAGCATG TCGTGTGGGG TGATGAAATG AAACCTTTGG CACGTTTGGC  
351 GGCCGCAGTG GAAATGGCCG GTGAATCAGA TAAAGCCAAC AGCCATATT  
401 TCGATGCGAT GGTTAATCAA AAAATCAATC TGGCCGATAC CGATACCCTG  
451 AAAAAATGGC TGTCCGAGCA AACAGCGTTT GACGGCAAAA AAGTATTGGC  
501 TGCATTTGAG GCTTCTGAAA GCCAAGCGCG TCGGGCTCAA ATGGAAGAGT

551 TGACCAATAA ATTCCAAATC AGCGGCACAC CGACTGTGAT CGTCGGCGGC

601 AAATACCAAG TTGAATTTAA AGACTGGCAG TCCGGTATGA CCACGATTGA

651 CCAGTTGGTG GATAAAGTAC GCGAAGAGCA GAAAAAGCCG CAATAA

FIGURE 12A (suite)

FIGURE 123

1 MKLKTALTS LTLALAACS KQAETSVPAD SVQSSSSAPA APAPLTEGVN

51 YTVLSTPIQ QQAGKVEVLE FFGYFCPHCA HLEPVLSEHI KTFKDDTYMR

101 REHVVGDEM KPLARLAAV EMAGESDKAN SHIFDAMVNQ KINLADTDTL

151 KKWLSEQTAF DGKKVLAAFE ASQSARAAQ MEELTNKFQI SGTPTVIVGG

201 KYQVEFKDWQ SGMTTIDQLV DKVREEQKKP Q\*

FIGURE 13a

1 ATGAAACTGA AACCTTAGC TTGACTTCA TTGACCCTGT TGGCATTGGC

51 CGCTTGTAGC AAACAGGCTG AAACCAGCGT TCCGGCAGAC AGCGTCCAAA

101 GCAGCTCATC TGCTCCGGCA GCCCCAGCCC CATTGACCGA AGGCGTGAAC

151 TAACTGTAT TGTCCACGCC TATCCGCAA CAGCAGGCCG GCAAAGTCGA

201 AGTCTTGAA TTTTTCGGCT ACTTCTGCCC GCATTGCGCC CATCTTGAGC

251 CGGTCTTGAG CGAGCACATC AAAACGTTTA AAGACGATAC CTATATGCGC

301 CGGGAGCATG TCGTGTGGGG TGATGAAATG AAACCTTTGG CACGTTTGGC

351 GGCCGCAGTG GAAATG GCCG GTGAATCAGA TAAAGCCAAC AGCCATATTT

401 TCGATGCGAT GGTTAATCAA AAAATCAATC TGGCCGATAC CGATACCTCG

451 AAAAAATGGC TGTCCGAGCA AACAGCGTTT GACGGCAAAA AAGTATTGGC

501 TGCATTTGAG GCTCCTGAAA GCCAAGCGCG TCGGGCTCAA ATGGAAGAGT

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551 TGACCAATAA ATTCCAAATC AGCGGCACAC CGACTGTGAT TGTCGGCGGC

601 AAATACCAAG TTGAATTTAA AGACTGGCAG TCCGGTATGA CCACGATTGA

651 CCAGTTGGTG GATAAAGTAC GCGAAGAGCA GAAAAAGCCG CAATAA

FIGURE 13A (suite)

FIGURE 13B

1 MKLKTALTS LTLLALAACS KQAETSVPAD SVQSSSSAPA APAPLTEGVN  
51 YTVLSTPIQ QQAGKVEVLE FFGYFCPHCA HLEPVLSEHI KTFKDDTYMR  
101 REHVVGDEM KPLARLAAAV EMAGESDKAN SHIFDAMVNQ KINLADTDTL  
151 KKWLSEQTAF DGKKVLAAFE APESQARAAQ MEELTNKFQI SGTPTVIVGG  
201 KYQVEFKDWQ SGMTTIDQLV DKVREEQKKP Q\*



Figure 14A

1 GAGTATGCTC TTAGAGAAAA ATTGATCAAA AAAGCCAAAG GGAAAGGCCT  
 51 ATTATCTTTA GATTGGGGCA GCCTGACCGA ACAAGAGGCA AGGCAGTTTA  
 101 TCTATTTGAT TGAGAAAGAT CGATATTCTA ATCAATTGCT TGACCGATAT  
 151 CAAAAAATC CAAGTAGTTT AAATAATCAA GAAAAAATA TTCTTGCATA  
 201 TTTTATTAAC CAAACCTCTG GAGGTAACAC AGCTTGGGCA GCTTCGATAC  
 251 TGAAAACGCC CCAGTCAATG GGTAACTCA CTATTCCTTC CAAAGATATT  
 301 AATAACACCT TATCGAAAGC CTATCAAACA TTGAGTCGTT ATGATTCTTT  
 351 TGATTACAAA TCAGCTGTTG CCGCACAACC TGCACTTTAC TTATTAAACG  
 401 GACCGCTTGG CTTCACTGTC AAAGCAGCTA CTGTGGCAGC AGGAGGATAT  
 451 AACATTGGAC AGGGAGCGAA AGCAATCTCT AATGGAGAAT ATCTGCATGG  
 501 TACAGTTCAG GTTGTTAATG GCACATTGAT GGTTCAGGA TCTGTATCTG  
 551 CACAGGCTGC AATATCGGCC AAGCTGCAC CTGTTACCCG TTATCTGAGC  
 601 AATGACAGTG CTCCTGCTTT AAGACAAGCT TTAAGTCTG AAAGCCAGAG  
 651 AATCCGCATG AAAGTCCGG AAGAGTATCG ACAAATAGGG AATCTTGCGA  
 701 TAGCAAAAAT TGATGTTAAA GGATTACCGC AAAGGATGGA AGCATTTAGT

751 TCTTTCCAAA AAGGGGAACA TGGATTTATT TCGTTACCTG AAACAAAAAT  
 801 TTTTAAACCT ATATCTGTTG ATAAATATCA TAATATTGCC TCTCCTCCTA  
 851 GAGGAACATT AAGAAATATA GATGGAGAAT ATAAATTACT TGAAACTATA  
 901 GCACAGCAAC TCGGAAATAA TCGTAATGTA TCAGGTAGAA TTGATCTATT  
 951 TACAGAATTA AAGGCCTGTC AATCTTGCAG CAATGTTATT TTAGAGTTTA  
 1001 GAAATCGCTA TCCAAATATT CAATTAAATA TTTTACAGG AAAATAG

**Figure 14A (suite)**

Figure 14B

1 EYALREKLIK KAKGKGLLSL DWGSLTEQEA RQFIYIEKD RYSNQLLDY  
51 QKNPSSLNNQ EKNLAYFIN QTSGGNTAWA ASILKTPQSM GNLTIPIKDI  
101 NNTLSKAYQT LSRYSDFDYK SAVAAQPALY LLNGPLGFSV KAATVAAGGY  
151 NIGQGAKAIS NGEYLHGTQ VVNGTLMVAG SVSAQAAISA KPAPVTRYLS  
201 NDSAPALRQA LTAESQRIRM KLPEEYRQIG NLAIAKIDVK GLPQRMFAFS  
251 SFQKGEHGFI SLPETKIFKP ISVDKYHNIA SPPRGTLRNI DGEYKLETI  
301 AQLGNRRNV SGRIDLTEK KACQSCSNVI LEFRNRYPMI QLNIFTGK

## FIGURE 15A

1 ATGAAAATAT CATTTCATTT AGCTTTATTA CCCACGCTGA TTATTGCTTC  
51 CTTCCCTGTT GCTGCCGCCG ATACGCAGGA CAATGGTGAA CATTACACCG  
101 CCACTCTGCC CACCGTTTCC GTGGTCGGAC AGTCCGACAC CAGCGTACTC  
151 AAAGGCTACA TCAACTACGA CGAAGCCGCC GTTACCCGCA ACGGACAGCT  
201 CATCAAAGAA ACGCCGCAAA CCATCGATAC GCTCAATATC CAGAAAAACA  
251 AAAATTACGG CACGAACGAT TTAGATTCCA TCCTCGAAGG CAATGCCGGC  
301 ATCGACGCCG CCTACGATAT GCGCGGCGAA AGCATTTTCC TGCGCGGCTT  
351 TCAAGCCGAC GCATCTGATA TTTACCGCGA CGGCGTACGC GAAAGCGGGC  
401 AGGTGCGCCG TAGCACCGCC AACATCGAGC GCGTGGAAT CCTGAAAGGT  
451 CCGTCTCCG TGCTTTATGG GCGTACCAAC GGCGGCGGTG TCATCAACAT  
501 GGTACAGCAA TACGCCAACT TCAAACAAAG CCGTAATATC GGTACGGTTT

551 ATGGTTCGTG GGC~~AA~~ACCGC AGCCTGAATA TGGACATCAA CGAAGTGCTG

601 AACAAAAACG TCGCCATCCG TCTACCGGC GAAGTCGGGC GCGCCAATTC

651 GTTCCGCAGC GGCATAGACA GCAAAAATGT CATGGTTTCG CCCAGCATT

701 CCGTCAAACG CGACAACCGC TTGAAGTGA CGGGGCAATA CACCTACGAC

751 AATGTGGAGC GCACGCCCGA CCGCAGTCCG ACCAAGTCCG TGTACGACCG

801 CTTCGGACTG CTTTACCGCA TGGGGTTCGC CCACCGGAAC GATTTTGTCA

851 AAGACAAGCT GCAAGTTTGG CGTTCCGACC TTGAATACGC CTTCAACGAC

901 AAATGGCGTG CCAATGGCA GCTCGCCAC CGCACGGCG CGCAGGATTT

951 TGATCATTTT TATGCAGGCA GCGAAAATGG CAACTTAATC AAACGTAAC

1001 ACGCCTGGCA GCAGACCGAC AACAAAACCC TGTCGTCAA CTTAACGCTC

1051 AACGGCGACT ACACCATCGG CCGTTTTGAA AACCACCTGA CCGTAGGCAT

1101 GGATTACAGC CGCGAACACC GCAACCCGAC ATTGGGTTTC AGCAGCGCCT

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1151 TTTCCGCCTC CATCAACCCC TACGACCGCG CAAGCTGGCC GGCTTCGGGC

1201 AGATTGCAGC CTATTCTGAC CCAAAACCGC CACAAAGCCG ACTCCTACGG

1251 CATCTTTGTG CAAAACATCT TCTCCGCCAC GCCCGATTTG AAATTCGTCC

1301 TCGGCGGCCG TTACGACAAA TACACCTTTA ATTCCGAAAA CAAACTCACC

1351 GGCAGCAGCC GCCAATACAG CGGACACTCG TTCAGCCCCA ACATCGGCGC

1401 AGTGTGGAAC ATCAATCCCG TCCACACACT TTACGCCTCG TATAACAAAG

1451 GCTTCGCGCC TTATGGCGGA CGCGGCGGCT ATTTGAGCAT CGATACGTTG

1501 TCTTCCGCCG TGTCAACGC CGACCCCGAG TACACCCGCC AATACGAAAC

1551 CGGCGTGAAA AGCAGTTGGC TGGACGACCG CCTCAGCACT ACGTTGTCTG

1601 CCTACCAAAT CGAACGCTTC AATATCCGCT ACCGCCCCGA TCCAAAAAAC

1651 AACCCTTATA TTTATGCGGT TAGCGGCAAA CACCGTTCGC GCGGCGTGGA

1701 ATTGTCCGCC ATCGGGCAAA TCATCCCCAA AAAACTCTAT CTGCGCGGTT

FIGURE 15A (suite 2)

1751 CGTTGGGCGT GATGCAGGCG AAAGTCGTTG AAGACAAAGA AAATCCCGAC  
1801 CGAGTGGGCA TCCATTTGAA TAACACCAGC AACGTTACCG GCAACCTGTT  
1851 TTTCCGTTAT ACCCCGACCG AAAACCTCTA CGGCGAAATC GGCCTAACCG  
1901 GTACAGGCAA ACGCTACGGT TACGACTCAA GAAATAAAGA AGTGACTACG  
1951 CTTCCAGGCT TTGCCCAGGT TGATGCCATG CTTGGCTGGA ACCATAAAAA  
2001 TGTTAACGTT ACCTTTGCCG CAGCCAATCT GTTCAATCAA AAATATTGGC  
2051 GTTCGGACTC TATGCCGGGT AATCCGCGCG GCTATACTGC CCGGGTAAAT  
2101 TACCGTTTCT GA

FIGURE 15A (suite 3)

## FIGURE 15B

1 MKISFHLALL PTLIASFPV AAADTQDNGE HYATLPTVS VVGQSDTSVL

51 KGYINYDEAA VTRNGQLIKE TPQTIDTLNI QKNKNYGTND LSSILEGNAG

101 IDAAYDMRGE SIFLRGFQAD ASDIYRDGVR ESGQVRRSTA NIERVEILKG

151 PSSVLYGRTN GGGVINMVSX YANFKQSRNI GTVYGSWANR SLNMDINEVL

201 NKNVAIRLTG EVGRANSFRS GDSKNVMVS PSITVKLDNG LKWTGQYTYD

251 NVERTPDOSP TKSVDYDFGL PYRMGFAHRN DFVKDKLQVW RSDLEYAFND

301 KWRAQWQLAH RTAAQDFDHF YAGSENGNLI KRNYAWQQTD NKTLSNLT

351 NGDYTIGRFE NHLTVGMDYS REHRNPTLGF SSAFSASINP YDRASWPASG

401 RLQPILTQNR HKADSYGIFV QNIFSATPDL KVLGGRYDK YTFENSENKL

451 GSSRQYSGHS FSPNIGAVWN INPVHTLYAS YNKGFPYGG RGGYLSIDTL

501 SSAVFNADPE YTRQYETGVK SSWLDDRLST TLSAYQIERF NIRYRPDPKN



551 NPYIYAVSGK HRSRGVELSA IGQIIPKKLY LRGSLGVMQA KVVEDKENPD

601 RVGIHLNNTS NVTGNLFFRY TPTENLYGEI GVTGTGKRYG YDSRNKEVTT

651 LPGFARVDAM LGWNHKNVNV TFAAANLFNQ KYWRSDSMPG NPRGYTARVN

701 YRF\*

FIGURE 15B (suite)

## FIGURE 16A

1 ATGAAAAATAT CATTTCATTT AGCTTTATTA CCCACGCTGA TTATTGCTTC  
51 CTTCCCTGTT GCTGCCGCCG ATACGCAGGA CAATGGTGAA CATTACACCG  
101 CCACTCTGCC CACCGTTTCC GTGGTCGGAC AGTCCGACAC CAGCGTACTC  
151 AAAGGCTACA TCAACTACGA CGAAGCCGCC GTTACCCGCA ACGGACAGCT  
201 CATCAAAGAA ACGCCGCAAA CCATCGATAC GCTCAATATC CAGAAAAACA  
251 AAAATTACGG CACGAACGAT TTGAGTTCCA TCCTCGAAGG CAATGCCGGC  
301 ATCGACGCCG CCTACGATAT GCGCGGCGAA AGCATTITTCC TGC GCGGCTT  
351 TCAAGCCGAC GCATCTGATA TTTACCGCGA CGGCGTACGC GAAAGCGGGC  
401 AGGTGCGCCG TAGCACC GCC AACATCGAGC GCGTGGAAT CCTGAAAGGT  
451 CCGTCCTCCG TGCTTTATGG GCGTACCAAC GGCGGCGGTG TCATCAACAT  
501 GGTACGCAAA TACGCCAACT TCAAACAAAG CCGTAATATC GGTACGGTTT

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551 ATGGTTCGTG GGCAAACCGC AGCCTGAATA TGGACATCAA CGAAGTGTCTG

601 AACAAAAACG TCGCCATCCG TCTACCCGGC GAAGTCGGGC GCGCCAATTC

651 GTTCCGCAGC GGCATAGACA GCAAAAATGT CATGGTTTCG CCCAGCATT A

701 CCGTCAAAC TCGACAACGGC TTGAAGTGA CGGGGCAATA CACCTACGAC

751 AATGTGGAGC GCACGCCCGA CCGCAGTCCG ACCAAGTCCG TGTACGACCG

801 CTTCGGACTG CTTACCGCA TGGGGTTCGC CCACCGGAAC GATTTTGTC A

851 AAGACAAGCT GCAAGTTTG CGTTCCGACC TTGAATACGC CTCAACGAC

901 AAATGGCGTG CCCAATGGCA GCTCGCCAC CGCACGGCGG CGCAGGATTT

951 TGATCATTT C TATGCAGGCA GCGAAAATGG CAACTTAATC AAACGTAAC T

1001 ACGCCTGGCA GCAGACCGAC AACAAAACCC TGTCGTCCAA CTTAACGCTC

1051 AACGGCGACT ACACCATCGG CCGTTTTGAA AACCACCTGA CCGTAGGCAT

1101 GGATTACAGC CGCGAACACC GCAACCCGAC ATTGGGTTTC AGCAGCGCCT

1151 TTTCCGCCTC CATCAACCCC TACGACCGCG CAAGCTGGCC GGCTTCGGGC

1201 AGATTGCAGC CTATTCTGAC CCAAACCGC CACAAAGCCG ACTCCTACGG

1251 CATCTTTGTG CAAACATCT TCTCCGCCAC GCCCGATTG AAATTCGTCC

1301 TCGGCGGCCG TTACGACAAA TACACCTTTA ATTCCGAAAA CAAACTCACC

1351 GGCAGCAGCC GCCAATACAG CGGACACTCG TTCAGCCCCA ACATCGGCGC

1401 AGTGTGGAAC ATCAATCCCG TCCACACACT TTACGCCTCG TATAACAAAG

1451 GCTTCGCGCC TTATGGCGGA CGCGGCGGCT ATTTGAGCAT CGATACGTTG

1501 TCTTCGCGCG TGTTCAACGC CGACCCCGAG TACACCCGCC AATACGAAAC

1551 CGGCGTGAAA AGCAGTTGGC TGGACGACCG CCTCAGCACT ACGTTGTCTG

1601 CCTACCAAAT CGAACGCTTC AATATCCGCT ACCGCCCCGA TCCAAAAAAC

1651 AACCCTTATA TTTATGCGGT TAGCGGCAAA CACCGTTCGC GCGGCGTGGA

1701 ATTGTCCGCC ATCGGGCAAA TCATCCCCAA AAAA ACTCTA TCTGCGCGGT

FIGURE 16.A (suite 2)

1751 TCGTTGGGCG TGATGCAGGC GAAAGTCGTT GAAGACAAAG AAAATCCCGA  
1801 CCGAGTGGGC ATCCATTTGA ATAACACCAG CAACGTTACC GGCAACCTGT  
1851 TTTTCCGTTA TACCCCGACC GAAAACCTCT ACGGCGAAAT CGGCGTAACC  
1901 GGTACAGGCA AACGCTACGG TTACGACTCA AGAAATAAAG AAGTGACTAC  
1951 GCTTCCAGGC TTTGCCCGAG TTGATGCCAT GCTTGGCTGG AACCATAAAA  
2001 ATGTTAACGT TACCTTTGCC GCAGCCAATC TGTTCATCA AAAATATTGG  
2051 CGTTCGGA CTATGCCGGG TAATCCGCGC GGCTATACTG CCCGGGTAAA  
2101 TTACCGTTTC TGA

FIGURE 16A (suite 3)

FIGURE 16B

1 MKISFHLALL PTLIASFPV AAADTQDNGE HYTATLPTVS VVGQSDTSVL

51 KGYINYDEAA VTRNGQLIKE TPQTIDTLNI QKNKNYGTND LSSILEGNAG

101 IDAAYDMRGE SIFLRGFQAD ASDIYRDGVR ESGQVRRSTA NIERVEILKG

151 PSSVLYGRTN GGGVINMVSK YANFKQSRNI GTVYGSWANR SLNMDINEVL

201 NKNVAIRLTG EVGRANSFRS GIDSKNMVS PSITVKLDNG LKWTGQYTYD

251 NVERTPDRSP TKSVDYDRFGL PYRMGFAHRN DFKDKLQVW RSDLEYAFND

301 KWRAQWQLAH RTAAQDFDHF YAGSENGNLI KRNYAWQQTD NKTLSNLTL

351 NGDYTIGRFE NHLTVGMDYS REHRNPTLGF SSAFSASINP YDRASWPASG

401 RLQPILTQNR HKADSYGIFV QNIFSATPDL KFLVGGRYDK YTFNSENKLT

451 GSSRQYSGHS FSPNIGAVWN INPVHTLYAS YNKGAFAPYGG RGGYLSIDTL

501 SSAVFNADPE YTRQYETGVK SSWLDDRLST TLSAYQIERF NIRYRPDPKN

551 NPYIYAVSGK HSRGVVELSA IGQIIPKKTL SARFVGRDAG ESR\*RQRKSR

601 PSGHPFE\*HQ QRYRQPVFPL YPDRKPLRRN RRNRYRQTLR LRLKK\*RS DY

651 ASRLCPS\*CH AWLEP\*KC\*R YLCRSQSVQS KILAFGLYAG \*SARLYCPGK

701 LPFL

FIGURE 16B (suite)

FIGURE 17A

1 ATGAAAATAT CATTTCA TTT AGCTTTATTA CCCACGCTGA TTATTGCTTC  
-----  
51 CTTCCCTGTT GCTGCCGCCG ATACGCAGGA CAATGGTGAA CATTACACCG  
101 CCACTCTGCC CACCGTTTCC GTGGTCGGAC AGTCCGACAC CAGCGTACTC  
151 AAAGGCTACA TCAACTACGA CGAAGCCGCC GTTACCCGCA ACGGACAGCT  
201 CATCAAAGAA ACGCCGCAAA CCATCGATAC GCTCAATATC CAGAAAAACA  
251 AAAATTACGG TACGAACGAT TTGAGTTCCA TCCTCGAAGG CAATGCCGGC  
301 ATCGACGCTG CCTACGATAT GCGCGGCGAA AGCATTTTCC TGC GCGGTTT  
351 TCAAGCCGAC GCATCCGATA TTTACCGCGA CGGCGTGCGC GAAAGCGGAC  
401 AAGTGCGCCG CAGTACTGCC AACATCGAGC GCGTGGAAT TCTGAAAGGC  
451 CCGTCTTCCG TGCTTTACGG CCGCACCAAC GCGGTGGCG TCATCAACAT  
501 GGTCAGCAAA TACGCCAACT TCAAACAAAG CCGCAACATC GGAGCGGTTT



551 ACGGCTCAAG GGCAAACCGC AGCCTGAATA TGGACATTAA CGAAGTGCTG

601 AACAAAAACG TCGCCATCCG TCTACCCGGC GAAGTCGGGC GCGCCAATTC

651 GTTCCGCAGC GGCATAGACA GCAAAAATGT CATGGTTTCG CCCAGCATT A

701 CCGTCAAAC TCGACAACGGC TTGAAGTGGA CGGGGCAATA CACCTACGAC

751 AATGTGGAGC GCACGCCCGA CCGCAGTCCG ACCAAGTCCG TGTACGACCG

801 CTTCGGACTG CTTACCGCA TGGGGTTCGC CCACCGGAAC GATTTTGTCA

851 AAGACAAGCT GCAAGTTTGG CGTTCCGACC TTGAATACGC CTTCAACGAC

901 AAATGGCGTG CCAATGGCA GCTCGCCAC CGCACGGCGG CGCAGGATTT

951 TGATCATTTT TATGCAGGCA GCGAAAATGG CAACTTAATC AAACGTAAC T

1001 ACGCCTGGCA GCAGACCGAC AACAAAACCC TGTCGTCAA TTTCAGGCTC

1051 AACGGCGACT ACACCATCGG CCGTTTTGAA AACCACTTGA CCGTAGGCAT

1101 GGATTACAGC CGCGAACACC GCAACCCGAC CTTAGGTTAC AGCCGCGCCT

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1151 T TACTGCTTC CATCGATCCA TACGACCGAG CAAGCTGGCC GGCTTCGGGC

1201 AGATTGCAGC CTATCCTCAC CAAAAACCGC CACAAAGCCG ACTCCTACGG

1251 CATCTTTGTG CAAAACATCT TCTCCGCCAC GCCCGATTG AAATTCGTCC

1301 TCGGCGGCCG TTACGACAAA TACACCTTTA ATTCCGAAAA CAAACTCACC

1351 GGCAGCAGCC GCCAGTACAG CGGCCACTCG TTCAGCCCCA ACATCGGCGC

1401 AGTGTGGAAC ATCAACCCCG TTCACACACT TTACGCCTCG TATAACAAAG

1451 GTTTCGCGCC TTATGGCGGA CGCGGCGGCT ATTTGAGCAT CGATACGTCA

1501 TCTTCTGCCG TGTTTAACGC CGACCCCGAG TACACCCGCC AATACGAAAC

1551 CGGCGTCAAA AGCAGTTGGC TGGACAATCG TTTGGACACC ACATTGTCCG

1601 CCTACCAAAT CGAACGCTTC AATATCCGCT ACCGCCCGCA CGCGGAAAAT

1651 AATCCCTACA CTGGGGCAGT CGGCGGCAAA CACCGTTCGC GTGGCGTGGA

1701 ATTGTCCGCC ATCGGGCAAA TCATCCCCAA AAAACTCTAT CTGCGCGGTT

FIGURE 17A (suite 2)

1751 CGTTGGGCGT GATGCAGGCG AAAGTCGTTG AAGACAAAAA AAATCCCGAC  
1801 CGAGTGGGCA TCCATTGAA TAATACCAGC AACGTTACCG GCAACCTGTT  
1851 TTTCCGTTAT ACCCGACCGA AAACCTCTAC GCGGAAATCG GCGTAACCGG  
1901 TACAGGCAAA CGCTACGGTT ACAACTCAAG AAATAAAGAA GTGACTACGC  
1951 TTCCAGGCTT TGCCCGAGTT GATGCCATGC TTGGCTGGAA CCATAAAAAAT  
2001 GTTAACGTTA CCTTTGCCGC AGCCAATCTG TTCAATCAAA AATATTGGCG  
2051 TTCGGACTCT ATGCCGGGTA ATCCGCGCGG CTATACTGCC CGGGTAAATT  
2101 ACCGTTTCTG A

FIGURE 17A (suite 3)

## FIGURE 17B

1 MKISFHLALL PTUIASFV AAADTQDNGE IYTATLPTVS VVGQSOTSVL  
51 KGYINYDEAA VTRNGQLIKE TPQTIDTLNI QKNKNYGTND LSSILEGNAG  
101 IDAAYDMRGE SIFLRGFQAD ASDIYRDGVR ESGQVRRSTA NIERVEILKG  
151 PSSVLYGRTN GGGVINMVSK YANFKQSRNI GAVYGSRRNR SLNMDINEVL  
201 NKNVAIRLTG EVGRANSFRS GIDSKNVMVS PSITVKLDNG LKWTGQYTYD  
251 NVERTPDRSP TKSVDYRFGI PYRMGFAHRN DFKDKLQVW RSDLEYAFND  
301 KWRAQWQLAH RTAAQDFDHF YAGSENGNLI KRNYAWQQTD NKTLSNFTL  
351 NGDYTIGRFE NHLTVGMDYS REHRNPTLGY SRAFTASIDP YDRASWPASG  
401 RLQPILTQNR HKADSYGIFV QNIFSATPDL KFLVGGRYDK YTFNSENKLT  
451 GSSRQYSGHS FSPNIGAVWN INPVHTLYAS YNKGFPYGG RGGYLSIDTS  
501 SSAVFNADPE YTRQYETGVK SSWLDNRLOD TLSAYQIERF NIRYRPAEN



FIGURE 18A

1 ATGAAAATAT CATTTCATTT AGCTTTATTA CCCACGCTGA TTATTGCTTC  
51 CTTCCCTGTT GCTGCCGCCG ATACGCAGGA CAATGGTGAA CATTACACCG  
101 CCACTCTGCC CACCGTTTCC GTGGTCGGAC AGTCCGACAC CAGCGTACTC  
151 AAAGGTACA TCAACTACGA CGAAGCCGCC GTTACCCGCA ACGGACAGCT  
201 CATCAAAGAA ACGCCGCAAA CCATCGATAC GCTCAATATC CAGAAAAACA  
251 AAAATTACGG TACGAACGAT TTGAGTTCCA TCCTCGAAGG CAATGCCGGC  
301 ATCGACGCTG CCTACGATAT GCGCGGCGAA AGCATTTTCC TGC GCGGTTT  
351 TCAAGCCGAC GCATCCGATA TTTACCGCGA CGGCGTGCGC GAAAGCGGAC  
401 AAGTGCGCCG CAGTACTGCC AACATCGAGC GCGTGAAAT CCTGAAAGGC  
451 CCGTCTTCCG TGCTTTACGG CCGCACCAAC GGC GCGGCGC TCATCAACAT  
501 GGTCAGCAAA TACGCCAACT TCAAACAAAG CCGCAACATC GGAGCGGTTT

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551 ACGGCTCATG GGCAAACCGC AGCCTGAATA TGGACATTAA CGAAGTGCTG

601 AACAAAAACG TCGCCATCCG TCTACCGGC GAAGTCGGGC GCGCCAATTC

651 GTTCCGCAGC GGCATAGACA GCAAAAATGT CATGGTTTCG CCCAGCATTA

701 CCGTCAAACG CGACAACGGC TTGAAGTGA CGGGGCAATA CACCTACGAC

751 AATGTGGAGC GCACGCCCGA CCGCAGTCCG ACCAAGTCCG TGTACGACCG

801 CTTCCGACTG CTTACCGCA TGGGGTTCG CCACCGGAAC GATTTTGTC A

851 AAGACAAGCT GCAAGTTTGG CGTTCCGACC TTGAATACGC CTTCAACGAC

901 AAATGGCGTG CCAATGGCA GCTCGCCAC CGCACGGCGG CGCAGGATTT

951 TGATCATTTT TATGCAGGCA GCGAAAATGG CAACTTAATC AAACGTAAC

1001 ACGCCTGGCA GCAGACCGAC AACAAAACCC TGTCGTCAA CTTAACGCTC

1051 AACGGCGACT ACACCATCGG CCGTTTTGAA AACCACTGA CCGTAGGCAT

1101 GGATTACAGC CGCGAACACC GCAACCCGAC ATTGGGTTTC AGCAGCGCCT

FIGURE 18A (suite 1)

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1151 TTTCCGCTC CATCAACCCC TACGACCGCG CAAGCTGGCC GGCTTCGGGC

1201 AGATTGCAGC CTATTCTGAC CAAAACCGC CACAAAGCCG ACGCCTACGG

1251 CATCTTTGTG CAAAACATCT TCTCCGCCAC GCCCGATTG AAATTCGTCC

1301 TCGGCGGTG TTACGACAAA TACACCTTTA ATTCCGAAAA CAAACTCACC

1351 GGCAGCAGCC GCCAATACAG CGGACACTCG TTCAGCCCCA ACATCGGCGC

1401 AGTGTGAAC ATCAATCCCG TCCACACACT TTACGCCTCG TATAATAAAG

1451 GCTTCGCGCC TTATGGCGGA CGCGGCGGCT ATTTGAGCAT CAACACGTG

1501 TCTTCGCGC TGTTCACGC CGACCCGAG TACACCCGCC AATACGAAAC

1551 CGGTGTGAAA AGCAGTTGGC TGGACGACCG CCTCAGCACT ACGTTGTCTG

1601 CCTACCAAAT CGAACGCTTC AATATCCGCT ACCGCCCCGA CGAGCAAAAT

1651 GATCCCTACA CTTGGGCAGT CGGCGGCAAA CACCGTTCGC GCGGCGTGGA

1701 ATTGTCCGCC ATCGGGCAAA TCATCCCCAA AAAACTCTAT CTGCGCGGTT

FIGURE 18A (suite 2)



1751 CGTTGGGCGT GATGCAGGCG AAAGTCGTTG AAGACAAAGA AAATCCCGAC  
1801 CGAGTGGGCA TCCATTTGAA TAACACCAGC AACGTTACCG GCAACCTGTT  
1851 TTTCCGTTAT ACCCCGACCG AAAACCTCTA CGGCGAAATC GGCCTAACCG  
1901 GTACAGGCAA ACGCTACGGT TACAACCTCAA GAAATAAAGA AGTGACTACG  
1951 CTTCCAGGCT TTGCCCAGT TGATGCCATG CTTGGCTGGA ACCATAAAAA  
2001 TGTTAACATT ACCTTTGCCG CAGCCAATCT GCTCAATCAA AAATATTGGC  
2051 GTTCGGATGC CATGCCCGGC GCGCCGCGCA CTTATACGGC GCGGGTTAAT  
2101 TACAGTTTCT AA

FIGURE 18A (suite 3)

## FIGURE 18B

1 MKISFHLALL PTUIASFPV AAADTQDNGE HYTATLPTVS VVGQSDTSVL  
51 KGYINYDEAA VTRNGQLIKE TPQTIDTLNI QKNKNYGTND LSSILEGNAG  
101 IDAAYDMRGE SIFLRGFQAD ASDIYRDGVR ESGQVRRSTA NIERVEILKG  
151 PSSVLYGRTN GGGVINMVS K YANFKQSRNI GAVYGSWANR SLNMDINEVL  
201 NKNVAIRLTG EVGRANSFRS GIDSKNVMVS PSITVKLONG LKWTGQYTYD  
251 NVERTPDRSP TKSVDYDRFGL PYRMGFAHRN DFKDKLQVW RSDLEYAFND  
301 KWRAQWQLAH RTAAQDFDHF YAGSENGNLI KKNYAWQQT D NKTLSNLT  
351 NGDYTIGRFE NHLTVGMDYS REHRNPTLGF SSAFSASINP YDRASWPASG  
401 RLQPILTQNR HKADAYGIFV QNIFSATPDL KFLVGGRYDK YTFNSENKLT  
451 GSSRQYSGHS FSPNIGAVWN INPVHTLYAS YNKGFPYGG RGGYLSINTS  
501 SSAVFNADPE YTRQYETGVK SSWLDDRLST TLSAYQIERF NIRYRPDEQN

551 DPYTWAVGGK HRSRGVELSA IGQIIPKKLY LRGLGVMQA KVVEDKENPD

601 RVGIHLNNTS NVTGNLFFRY TPTENLYGEI GVTGTGKRYG YNSRNKEVTT

651 LPGFARVDAM LGWNHKNVNI TFAAANLLNQ KYWRSDAMPG APRTYTARVN

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FIGURE 18B (suite)

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FIGURE 19A

1 ATGAAAATAT CATTTTCATT AGCTTTATTA CCCACGCTGA TTATTGCTTC

51 CTTCCCTGTT GCTGCCGCCG ATACGCAGGA CAATGGTGAA CATTACACCG

101 CCACTCTGCC CACCGTTTCC GTGGTCGGAC AGTCCGACAC CAGCGTACTC

151 AAAGGTACA TCAACTACGA CGAAGCCGCC GTTACCCGCA ACGGACAGCT

201 CATCAAAGAA ACGCCGCAAA CCATCGATAC GCTCAATATC TAGAAAAACA

251 AAAATTACGG TACGAACGAT TTGAGTTCCA TCCTCGAAGG CAATGCCGGC

301 ATCGACGCTG CCTACGATAT GCGCGGCGAA AGCATTTTCC TGCGCGGTTT

351 TCAAGCCGAC GCATCCGATA TTTACCGCGA CGGCGTGCGC GAAAGCGGAC

401 AAGTGCGCCG CAGTACTGCC AACATCGAGC GCGTGGAAT CCTGAAAGGC

451 CCGTCTTCG TGCTTTACGG CCGCACCAAC GCGGCGGCG TCATCAACAT

501 GGTCAGCAAA TACGCCAACT TCAAACAAAG CCGCAACATC GGTGCGGTTT

WO 01/04150

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551 ACGGTTCTGT GGCAAACCGC AGCCTGAATA TGGACATTAA CGAAGTGTTG

601 AACAAAAACG TCGCCATCCG TCTACCCGGC GAAGTCGGGC GCGCCAATTC

651 GTTCCGCAGC GGCATAGACA GCAAAAATGT CATGGTTTCG CCCAGCATTA

701 CCGTCAAACCT CGACAACGGC TTGAAGTGGA CGGGGCAATA CACCTACGAC

751 AATGTGGAGC GCACGCCCGA CCGCAGTCCG ACCAAGTCCG TGTACGACCG

801 CTTCGGACTG CTTACCGCA TGGGGTTCGC CCACCGGAAC GATTTTGTCA

851 AAGACAAGCT GCAAGTTTGG CGTCCGACC TTGAATACGC CTCAACGAC

901 AAATGGCGTG CCAATGGCA GCTCGCCAC CGCACGGCGG CGCAGGATTT

951 TGATCATTTT TATGCAGGCA GCGAAAATGG CAACTTAATC AAACGTAAC

1001 ACGCCTGGCA GCAGACCGAC AACAAAACCC TGTCTCCAA TTTCACGCTA

1051 AACGGCGACT ACACCATCGG CCGTTTTGAA AACCACTTGA CCGTAGGCAT

1101 GGATTACAGC CGCGAACACC GCAACCCGAC CTTAGGTTAC AGCCGCGCCT

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1151 TTACTGCTTC CATCGATCCA TACGACCGAG CAAGCTGGCC GGCTTCGGGC

1201 AGATTGCAGC STATCCTCAC CCAAACCGC CACAAAGCCG ACTCCTACGG

1251 CATCTTTGTG CAAAACATCT TCTCCGCCAC GCCCGATTG AAATTCGTCC

1301 TCGGCGGTCG TTACGACAAA TACACCTTTA ATTCCGAAAA CAAACTCACC

1351 GGCAGCAGCC GCCAATACAG CGGACACTCG TTCAGCCCCA ACATCGGCGC

1401 AGTGTGGAAC ATCAATCCCG TCCACACACT TTACGCCTCG TATAATAAAG

1451 GCTTCGCGCC TTATGGCGGA CGCGGCGGCT ATTTGAGCAT CAACACGTGC

1501 TCTTCGCGG TGTCAACGC CGACCCCGAG TACACCCGCC AATACGAAAC

1551 CGGTGTGAAA AGCAGTTGGC TGGACGACCG CCTCAGCACT ACGTTGTCTG

1601 CCTACCAAAT CGAACGCTTC AATATCCGCT ACCGCCCGA CGAGCAAAAT

1651 GATCCCTACA CTTGGGCAGT CGGCGGCAAA CACCGTTCGC GCGGCGTGGA

1701 ATTGTCCGCC ATCGGGCAAA TCATCCCCAA AAAACTCTAT CTGCGCGGTT

FIGURE 19A (suite 2)

1751 CGTTGGGCGT GATGCAGGCG AAAGTCGTTG AAGACAAAGA AAATCCCGAC  
1801 CGAGTGGGCA TCCATTTGAA TAACACCAGC AACGTTACCG GCAACCTGTT  
1851 TTTCCGTTAT ACCCCGACCG AAAACCTCTA CGGCGAAATC GGC GTAACCG  
1901 GTACAGGCAA ACGCTACGGT TACAAC TCAA GAAATAAAGA AGTGACTACG  
1951 CTTCCAGGCT TTGCCCGAGT TGATGCCATG CTTGGCTGGA ACCATAAAAA  
2001 TGTTAACATT ACCTTTGCCG CAGCCAATCT GCTCAATCAA AAATATTGGC  
2051 GTTCGGATGC CATGCCCGGC GCGCCGCGCA CTTATACGGC GCGGGTTAAT  
2101 TACAGTTTCT AA

FIGURE 19A (suite 3)

## FIGURE 19B

1 MKISFHLALL PTLIIASFPV AAADTQDNGE HYTATLPTVS VVGQSDTSVL

51 KGYINYDEAA VTRNGQLIKE TPQTIDTLNI \*KNKNYGTND LSSILEGNAG

101 IDAAYDMRGE SIFLRGFQAD ASDIYRDGVR ESGQVRRSTA NIERVEILKG

151 PSSVLYGRTN GGGVINMVSK YANFKQSRNI GAVYGSWANR SLNMDINEVL

201 NKNVAIRLTG EVGRANSFRS GIDSKNVMVS PSITVKLDNG LKWTGQYTYD

251 NVERTPDRSP TKSVDYRFGI PYRMGFAHRN DFKDKLQVW RSDLEYAFND

301 KWRAQWQLAH RTAAQDFDHF YAGSENGNLI KRNYAWQQTD NKTLSNFTL

351 NGDYTIGRFE NHLTVGMDYS REHRNPTLGY SRAFTASIDP YDRASWPASG

401 RLQPILTQNR HKADSYGIFV QNIFSATPDL KFVLGGRYDK YTFNSENKLT

451 GSSRQYSGHS FSPNIGAVWN INPVHTLYAS YNKGFPYGG RGGYLSINTS

501 SSAVFNADPE YTRQYETGVK SSWLDDRLST TLSAYQIERF NIRYRPDEQN



551 DPYTWAVGGK HRSRGVELSA IGQIIPKKLY LRGSLGVMQA KVVEDKENPD

601 RVGIHLNNTS NVTGNLFFRY TPTENLYGEI GVTGTGKRYG YNSRNKEVTT

651 LPGFARVDAM LGWNHKNVNI TFAAANLLNQ KYWRSDAMPG APRTYTARVN

701 YSF\*

FIGURE 19B (suite)

## FIGURE 20A

1 ATGAAAATAT CATTTCATTT AGCTTTATTA CCCACGCTGA TTATTGCTTC  
51 CTTCCCTGTT GCTGCCGCCG ATACGCAGGA CAATGGTGAA CATTACACCG  
101 CCACTCTGCC CACCGTTTCC GTGGTCGGAC AGTCCGACAC CAGCGTACTC  
151 AAAGGCTACA TCAACTACGA CGAAGCCGCC GTTACCCGCA ACGGACAGCT  
201 CATCAAAGAA ACGCCGCAAA CCATCGATAC GCTCAATATC TAGAAAAACA  
251 AAAATTACGG TACGAACGAT TTGAGTTCCA TCCTCGAAGG CAATGCCGGC  
301 ATCGACGCTG CCTACGATAT GCGCGGCGAA AGCATTTTCC TGC GCGGTTT  
351 TCAAGCCGAC GCATCCGATA TTACCGCGA CGGCGTGCGC GAAAGCGGAC  
401 AAGTGCGCCG CAGTACTGCC AACATCGAGC GCGTGGAAAT CCTGAAAGGC  
451 CCGTCTTCG TGCTTTACGG CCGCACCAAC GGCGGCGGCG TCATCAACAT  
501 GGTCAGCAAA TACGCCAACT TCAAACAAAG CCGCAACATC GGTGCGGTTT

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551 ACGGTTCTGT GGCAAACCGC AGCCTGAATA TGGACATTAA CGAAGTGTTG

601 AACAAAAACG TCGCCATCCG TCTACCGGC GAAGTCGGGC GCGCCAATTC

651 GTTCCGCAGC GGCATAGACA GCAAAAATGT CATGGTTTCG CCCAGCATTA

701 CCGTCAAACG CGACAACGGC TTGAAGTGGA CGGGGCAATA CACCTACGAC

751 AATGTGGAGC GCACGCCCGA CCGCAGTCCG ACCAAGTCCG TGTACGACCG

801 CTTGGGACTG CTTACCGCA TGGGGTTCGC CCACCGGAAC GATTTTGTC A

851 AAGACAAGCT GCAAGTTTG CGCTCCGACC TTGAATACGC CTTCAACGAC

901 AAATGGCGTG CCAATGGCA GCTCGCCAC CGCACGGCGG CGCAGGATTT

951 TGATCATTTT TATGCAGGCA GCGAAAATGG CAACTTAATC AAACGTAAC T

1001 ACGCCTGGCA GCAGACCGAC AACAAAACCC TGTCGTCCAA TTTCACGCTA

1051 AACGGCGACT ACACCATCGG CCGTTTTGAA AACC ACTTGA CCGTAGGCAT

1101 GGATTACAGC CGCGAACACC GCAACCCGAC ATTGGGCTAC CGCGGCAGTT

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1151 TCACCGTGCC CATCAACCCC TACGACCGCG CAAGCTGGCC GGCTTCGGGG

1201 AGATTGCAGC CTATTCTGAC CAAAACCGC CACAAAGCCG ACTCCTACGG

1251 CATCTTTGTG CAAAACATCT TCTCCGCTAC GCCCGATTG AAATTCGTCC

1301 TCGGCGGCCG TTACGACAAA TACACCTTTA ATTCCGAAAA CAAACTCACC

1351 GGCAACAGCC GCCAATACAG CGGACACTCG TTCAGCCCCA ACATCGGCGC

1401 AGTGTGGAAC ATCAACCCAG TCCACACACT TTACGCCTCG TATAACAAAG

1451 GCTTCGCGCC TTATGGCGGA CGCGCGGCT ATTTGAGTAT CGATACGTTG

1501 TCTTCGCGCC TGTTC AACGC CGACCCGAG TACACCCGCC AATACGAAAC

1551 CGGCGTGAAA AGCAGTTGGC TGGACGACCG CCTCAGCACC ACATTGTCCG

1601 CCTACCAAAT CGAACGCTTC AATATCCGCT ACCGCCCGA TCCAAAAAAC

1651 AACCCTTATA TTTATGCGGT TAGCGGCAAA CACCGTTCGC GCGGCGTGGA

1701 ATTGTCCGCC ATCGGGCAAA TCATCCCCAA AAAACTCTAT CTGCGCGGTT

1751 CGTTGGGCGT GATGCAGGCG AAAGTCGTG AAGACAAAGA AAATCCCGAC  
1801 CGAGTGGGCA TCCATTTGAA TAATACCAGC AACGTTACCG GCAACCTGTT  
1851 TTTCCGTTAT ACCCCGACCG AAAACCTCTA CGGCGAAATC GGCCTAACCG  
1901 GTACAGGCAA ACGCTACGGT TACAACTCAA GAAATAAAGA AGTGACTACG  
1951 CTTCAGGCT TTGCCCAGT TGATGCCATG CTTGGCTGGA ACCATAAAAA  
2001 TGTTAACGTT ACCTTTGCCG CAGCCAATCT GTTCAATCAA AAATATTGGC  
2051 GTTCGGACTC TATGCCGGGT AATCCGCGCG GCTATACTGC CCGGGTAAAT  
2101 TACCGTTTCT GA

FIGURE 20A (Suite 3)

## FIGURE 20B

1 MKISFHLALL PTLIASFPV AAADTQDNGE HYTATLPTVS VVGQSDTSVL  
51 KGYINYDEAA VTRNGQLIKE TPQTIDTLNI \*KNKNYGTND LSSILEGNAG  
101 IDAAYDMRGE SIFLRGFQAD ASDIYRDGVR ESGQVRRSTA NIERVEILKG  
151 PSSVLYGRTN GGGVINMVSK YANFKQSRNI GAVYGSWANR SLNMDINEVL  
201 NKNVAIRLTG EVGRANSFRS GIDSKNMVMS PSITVKLDNG LKWTGQYTYD  
251 NVERTPDRSP TKSVYDRFGL PYRMGFAHRN DFKVDKLQVW RSDLEYAFND  
301 KWRAQWQLAH RTAAQDFDHF YAGSENGNLI KRNYAWQQTD NKTLSNFTL  
351 NGDYTIGRFE NHLTVGMDYS REHRNPTLGY RGSFTVPINP YDRASWPASG  
401 RLQPILTQNR HKADSYGIFV QNIFSATPDL KVLGGGRYDK YTFNSENKLT  
451 GNSRQYSGHS FSPNIGAVWN INPVHTLYAS YNKGFPYGG RGGYLSIDTL  
501 SSAVFNADPE YTRQYETGVK SSWLDDRLST TLSAYQIERF NIRYRPDPKN

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551 NPYIYAVSGK HRSRGVELSA IGQIIPKKLY LRGSLGVMQA KVVEDKENPD

601 RVGIHLNNTS NVTGNLFFRY TPTENLYGEI GVTGTGKRYG YNSRNKEVTT

651 LPGFARVDAM LGWNHKNVNV TFAAANLFNQ KYWRSDSMPG NPRGYTARVN

701 YRF\*

FIGURE 20B (suite)

## FIGURE 21A

1 ATGAAAATAT CATTTCATTT AGCTTTATTA CCCACGCTGA TTATTGCTTC  
51 CTTCCCTGTT GCTGCCGCCG ATACGCAGGA CAATGGTGAA CATTACACCG  
101 CCACTCTGCC CACCGTTTCC GTGGTCGGAC AGCCGACAC CAGCGTACTC  
151 AAAGGCTACA TCAACTACGA CGAAGCCGCC GTTACCCGCA ACGGACAGCT  
201 CATCAAAGAA ACGCCGCAAA CCATCGATAC GCTCAATATC CAGAAAAACA  
251 AAAATTACGG TACGAACGAT TTGAGTTCCA TCCTCGAAGG CAATGCCGGC  
301 ATCGACGCTG CCTACGATAT GCGCGGCGAA AGCATTTTCC TCGCGGTTTT  
351 TCAAGCCGAC CATCCGATA TTTACCGCGA CGGCGTGCGC GAAAGCGGAC  
401 AAGTGCGCCG CAGTACTGCC AACATCGAGC GCGTGGAAT CCTGAAAGGC  
451 CCGTCTTCG TGCTTTACGG CCGCACCAAC GCGGGCGGCG TCATCAACAT  
501 GGTCAGCAAA TACGCCAACT TCAAACAAAG CCGCAACATC GGTGCGGTTT



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551 ACGGTTAGTG GGC~~AA~~ACCGC AGCCTGAATA TGGACATTAA CGAAGTGCTG

601 AACAAAAACG TCGCCATCCG TCTACCCGGC GAAGTCGGGC GCGCCAATTC

651 GTTCCGCAGC GGCATAGACA GCAAAAATGT CATGGTTTCG CCCAGCATTAA

701 CCGTCAAACCT CGACAACGGC TTGAAGTGGG CGGGGCAATA CACCTACGAC

751 AATGTGGAGC GCACGCCCGA CCGCAGTCCG ACCAAGTCCG TGTACGACCG

801 CTTCGGACTG CCTTACCGCA TGGGGTTCGC CCACCGGAAC GATTTTGTCA

851 AAGACAAGCT GCAAGTTTGG CGTTCCGACC TTGAATACGC CTTCACGAC

901 AAATGGCGTG CCAATGGCA GCTCGCCAC CGCACGGCGG CGCAGGATTT

951 TGATCATTTT TATGCAGGCA GCGAAAATGG CAACTTAATC AAACGTAAC

1001 ACGCCTGGCA GCAGACTGAC AACAAAACCC TGTCGTCCAA TTTCACGCTA

1051 AACGGCGACT ACACCATCGG CCGTTTTGAA AACCACCTGA CCGTAGGCAT

1101 GGATTACAGC CGCGAACACC GCAACCCGAC CTTAGGTTAC AACCGCGCCT

FIGURE 21A (suite 1)

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1151 TTTCCGCCTC CATCAACCCC TACGACCGCG CAAGCTGGCC GGCTTCGGGC

1201 AGATTGCAGC CTATTCTGAC CCAAAACCGC CACAAAGCCG ACTCCTACGG

1251 CATCTTTGTG CAAAACATCT TCTCGCCAC GCCCGATTG AAATTCGTCC

1301 TCGGCGGCCG TTACGACAAA TACACCTTTA ATTCGAAAA CAAACTCACC

1351 GGCAGCAGCC GCCAATACAG CGGACACTCG TTCAGCCCCA ACATCGGCGC

1401 AGTGTGGAAC ATCAATCCCG TCCACACACT TTACGCCTCG TATAACAAAG

1451 GCTTCGCGCC TTATGGCGGA CGCGGCGGCT ATTTGAGCAT CGATACGTTG

1501 TCTTCGCGCG TGTTCACGC CGACCCCGAG TACACCGCC AATACGAAAC

1551 CGGCGTGAAA AGCAGTTGGC TGGACGACCG CCTCAGCACT ACGTTGTCTG

1601 CCTACCAAAT CGAACGCTTC AATATCCGCT ACCGCCCCGA TCCAAAAAAC

1651 AACCCTTATA TTTATGCGGT TAGCGGCAAA CACCGTTCGC GCGGCGTGGA

1701 ATTGTCGCGC ATCGGGCAAA TCATCCCTAA AAAACTCTAT CTGCGCGGTT

1751 CGTTGGGCGT GATGCAGGCG AAAGTCGTTG AAGACAAAGA AAATCCCGAC

1801 CGAGTGGGCA TCCATTTGAA TAACACCAGC AACGTTACCG GCAACCTGTT

1851 TTTCCGTAT ACCCCGACCG AAAACCTCTA CGGCGAAATC GGCGTAACCG

1901 GTACAGGCAA ACGCTACGGT TACGACTCAA GAAATAAAGA AGTGACTACG

1951 CTTCCAGGCT TTGCCCAGT TGATGCCATG CTTGGCTGGA ACCATAAAAA

2001 TGTTAACGTT ACCTTTGCCG CAGCCAATCT GTTCAATCAA AAATATTGGC

2051 GTTCGGACTC TATGCCGGT AATCCGCGCG GCTATACTGC CCGGGTAAAT

2101 TACCGTTTCT GA

FIGURE 21A (suite 3)

## FIGURE 21B

1 MKISFHLALL PTLIIASFPV AAADTQDNGE HYTATLPTVS VVGQSDTSVL  
51 KGYINYDEAA VTRNGQLIKE TPQTIDTLNI QKNKNYGTND LSSILEGNAG  
101 IDAAYDMRGE SIFLRGFQAD ASDIYRDGVR ESGQVRRSTA NIERVEILKG  
151 PSSVLVGRTN GGGVINMVSK YANFKQSRNI GAVYG\*WANR SLNMDINEVL  
201 NKNVAIRLTG EVGRANSFRS GIDSKNMVS PSITVKLNG LKWTGQYTYD  
251 NVERTPDRSP TKSVDYDRFGL PYRMGFAHRN DFKDKLQVW RSDLEYAFND  
301 KWRAQWQLAH RTAAQDFDHF YAGSENGNLI KRNYAWQQTD NKTLSNFTL  
351 NGDYTIGRFE NHLTVGMDYS REHRNPTLG Y NRAFTASINP YDRASWPASG  
401 RLQPILTQNR HKADSYGIFV QNIFSATPDL KFMLGGRYDK YTFNSENKLT  
451 GSSRQYSGHS FSPNIGAVWN INPVHTLYAS YNKGAFAPYGG RGGYLSIDTL  
501 SSAVFNADPE YTRQYETGVK SSWLDDRLST TLSAYQIERF NIRYRDPKKN

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551 NPYIYAVSGK HSRGVELSA IGQIPKKLY LRGLGVMQA KVVEDKENPD

601 RVGIHLNNTS NVTGNLFFRY TPTENLYGEI GVTGTGKRYG YDSRNKEVTT

651 LPGFARVDAM LGWNHKNVNV TFAAANLFNQ KYWRSDSMPG NPRGYTARVN

701 YRF\*

FIGURE 21B (suite)

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FIGURE 22A

1 ATGAAAATAT CATTTTCATT AGCTTTATTA CCCACGCTGA TTATTGCTTC  
 51 CTTCCCTGTT GCTGCCGCCG ATACGCAGGA CAATGGTGAA CATTACACCG  
 101 CCACTCTGCC CACCGTTTCC GTGGTCGGAC AGTCCGACAC CAGCGTACTC  
 151 AAAGGCTACA TCAACTACGA CGAAGCCGCC GTTACCCGCA ACGGACAGCT  
 201 CATCAAAGAA ACGCCGCAAA CCATCGATAC GCTCAATATC CAGAAAAACA  
 251 AAAATTACGG TACGAACGAT TTGAGTTCCA TCCTCGAAGG CAATGCCGGC  
 301 ATCGACGCTG CCTACGATAT GCGCGGTGAA AGCATTTTCC TGCGCGGTTT  
 351 TCAAGCCGAC GCATCCGATA TTTACCGCGA CGGCGTGCGC GAAAGCGGAC  
 401 AAGTGCGCCG CAGTACTGCC AACATCGAGC GCGTGGAAT CCTGAAAGGC  
 451 CCGTCTTCCG TGCTTTACGG CCGCACCAAC GCGGGCGGCG TCATCAACAT  
 501 GGTGAGCAAA TACGCCAACT TCAAACAAAG CCGCAACATC GGTGCGGTTT







1751 TGGGCGTGAT GCAGGCGAAA GTCGTTGAAG ACAAAGAAAA TCCCGACCGA  
1801 GTGGGCATCC ATTTGAATAA CACCAGCAAC GTTACCGGCA ACCTGTTTTT  
1851 CCGTTATACC CCGACTGAAA ACCTCTACGG CGAAATCGGC GTAACCGGTA  
1901 CAGGCAAACG CTACGGCTAC AACTCAAGAA ATAAAGAAGT GACCACGCTT  
1951 CCAGGCTTTG CCCGAGTTGA TGCCATGCTC GGCTGGAACC ATAAAAATGT  
2001 TAACGTTACC TTTGCCGCTG CCAATCTGCT CAATCAAAAA TATTGGCGTT  
2051 CGGACTCTAT GCCGGGTAAT CCGCGCGGCT ATACTGCCCG GGTA AATTAC  
2101 CGTTTCTGA

FIGURE 22A (suite 3)

## FIGURE 22B

1 MKISFHLALL PTLIIASFPV AAADTQDNGE HYTATLPTVS VVGQSDTSVL  
51 KGYINYDEAA VTRNGQLIKE TPQTIDTLNI QKNKNYGTND LSSILEGNAG  
101 IDAAYDMRGE SIFLRGFQAD ASDIYRDGVR ESGQVRRSTA NIERVEILKG  
151 PSSVLYGRTN GGGVINMVS K YANFKQSRNI GAVYGSWANR SLNMDINEVL  
201 NKNVAIRLTG EVGRANSFRS GIDSKNVMVS PSITVKLDNG LKWTGQYTYD  
251 NVERTPDRSP TKSVDYDRFGL PYRMGFAHRN DFKDKLQVW RSDLEYAFND  
301 KWRAQWQLAH RTAAQDFDHF YAGSENGNLI KRNYAWQQT D NKTLSNLTL  
351 NGDYTIGRFE NHLTVGMDYS REHRNPTLGY RGSFTVPINP YDRASWPASG  
401 RLQPILTQNR HKADSYGIFV QNIFSATPDL KVLGGRYDK YTFNSENKLT  
451 GNSRQYSGHS FSPNIGAVWN INPVHTLYAS YNKGFPYGG RGYLSIDTSS  
501 AAVFNAAPEY TRQYETGVKS SWLDDRLSTT LSAYQIERFN IRYRPDPKNN

551 PYIYAVSGKH RSRGVELSAI GQIIPKKLYL RGS LGVMQAK VVEDKENPDR

601 VGIHLNNTSN VTGNLFFRYT PTENLYGEIG VTGTGKRYGY NSRNKEVTTL

651 PGFARVDAML GWNHKNVNVF FAAANLLNQK YWRSDSMPGN PRGYTARVNY

701 RF\*

FIGURE 22B (suite)

## FIGURE 23A

1 ATGAAAAATAT CATTTTCATTT AGCTTTATTA CCCACGCTGA TTATTGCTTC  
51 CTTCCCTGTT GCTGCCGCCG ATACGCAGGA CAATGGTGAA CATTACACCG  
101 CCACGCTACC TACCGTTTCC GTGGTCGGAC AGTCCGACAC CAGCGTACTC  
151 AAAGGCTACA TCAACTACGA CGAAGCCGCC GTTACCCGCA ACGGACAGCT  
201 CATCAAAGAA ACGCCGCAAA CCATCGATAC GCTCAATATC CAGAAAAACA  
251 AAAATTACGG CACGAACGAT TTGAGTTCCA TCCTCGAAGG CAATGCCGGC  
301 ATCGACGCTG CCTACGATAT GCGCGGTGAA AGCATTTTCC TGC GCGGTTT  
351 TCAAGCCGAC GCATCCGATA TTTACCGCGA CGGCGTGCGC GAAAGCGGAC  
401 AAGTGCGCCG CAGTACTGCC AACATCGAGC GCGTGGAAT CCTGAAAGGC  
451 CCGTCTTCCG TGCTTTACGG CCGTACCAAC GCGGCGGCG TCATCAACAT  
501 GGTCAGCAAA TACGCCAACT TCAAACAAAG CCGCAACATC GGTGCGGTTT



1151 TCACCGTGCC CATCAACCCC TACGACCGCG CAAGCTGGCC GGCTTCGGGC

1201 AGATTGCAGC CTATTCTGAC CCAAACCGC CACAAAGCCG ACTCCTACGG

1251 CATCTTTGTG CAAAACATCT TCTCCGCTAC GCCCGATTG AAATTCGTCC

1301 TCGGCGGCCG TTACGACAAA TACACCTTTA ATTCCGAAAA CAAACTCACC

1351 GGCAACAGCC GCCAATACAG CGGACACTCG TTCAGCCCCA ACATCGGCGC

1401 AGTGTTGAAC ATCAACCCAG TCCACACACT TTACGCCTCG TATAACAAAG

1451 GCTTCGCGCC TTATGGCGGA CGCGGATATT TGAGTATCGA CACTTCGTCT

1501 GCCGCCGTGT TCAACGCCGC CCCCAGGTAC ACCCCCAATA CGAAACCGGC

1551 GTCAAAAGCA GTTGGCTGGA CAATCGTTTG GACACCACCC TGTCGGTTTA

1601 CCAAAATCGAA CGCTTCAATA TCCGCTACCG CCCCAGTCCA AAAAACAACC

1651 CTTATATTTA TCGGTTAGC GGCAAACACC GTTCGCGCGG CGTGAATTG

1701 TCCGCCATCG GGCAAATCAT CCCCACAAAA CTCTATCTGC GCGGTTCTGT

1751 GGGCGTGATG CAGGCGAAAAG TCGTTGAAGA CAAAGAAAAT CCCGACCGAG  
1801 TGGGCATCCA TTTGAATAAC ACCAGCAACG TTACCGGCAA CCTGTTTTTC  
1851 CGTTATACCC CGACCGAAAA CCTCTACGGC GAAATCGGCG TAACCGGTAC  
1901 GGGCAAACGC TACGGTTACA ACTCAAGAAA TAAAGAAGTG ACTACGCTTC  
1951 CAGGCTTTGC CCGAGTTGAT GCCATGCTTG GCTGGAACCA TAAAAATGTT  
2001 AACGTTACCT TTGCCGCAGC CAATCTGTTC AATCAAAAAT ATTGGCGTTC  
2051 GGA CTCTATG CCGGGTAATC CGCGCGGCTA TACTGCCCCG GTAAATTACC  
2101 GTTCTGA

FIGURE 23A (suite 3)

## FIGURE 23B

1 MKISFHLALL PTLIASFPV AAADTQDNGE HYTATLPTVS VVGQSDTSVL  
51 KGYINYDEAA VTRNGQLIKE TPQTIDTLNI QKNKNYGTND LSSILEGNAG  
101 IDAAYDMRGE SIFLRGFQAD ASDIYRDGVR ESGQVRRSTA NIERVEILKG  
151 PSSVLYGRTN GGGVINMVS K YANFKQSRNI GAVYGSWANR SLNMDINEVL  
201 NKNVAIRLTG EVGRANSFRS GIOSKNVMVS PSITVKLDNG LKWTGQYTYD  
251 NVERTPDOSP TKSVDYDRFGL PYRMGFAHPN DFKVDKLQVW RSDLEYAFND  
301 KWRAQWQLAH RTAAQDFDHF YAGSENGSRI KRNYAWQQTD NKTLSNFTL  
351 NGDYTIGRFE NHLTVGMOYS REHRNPTLG Y RGSFTVPINP YDRASWPASG  
401 RLQPILTQNR HKADSYGIFV QNIFSATPDL KFVLGGRYDK YTFNSENKLT  
451 GNSRQYSGHS FSPNIGAVWN INPVHTLYAS YNKGFPYGG RGYLSIDTSS  
501 AAVFNAAPEY TPNTKPASKA VGWTIVWTPP CRFTKSNASI SATAPIQKTT



551 LIFMRLAANT VRAAWNCPPS GKSSPKNSIC AVRWA\*CRRK SLKTKKIPT

601 WASI\*ITPAT LPATCFSVIP RPKTSTAKSA \*PVRANATVT TQEIKK\*LRF

651 QALPELMPCL AGTIKMLTLP LPQPICSIKN IGVRTLRCVI RAAILPG\*IT

701 VS

FIGURE 23B (suite)

## FIGURE 24A

1 ATGCAAATAC CATTTCATTT GGCTTTATTA CCCACGCTGA TTATTGCTTC  
51 CTTCCTGTG GCTGCCGCCG ATACGCAGGA CAATGGTGAA CATTACACCG  
101 CCACGCTACC TACCGTTTCC GTGGTCGGAC AGTCCGACAC CAGCGTACTC  
151 AAAGGCTACA TCAACTACGA CGAAGCCGCC GTTACCCGCA ACGGACAGCT  
201 CATCAAAGAA ACGCCGCAAA CCATCGATAC GCTCAATATC CAGAAAAACA  
251 AAAATTACGG CACGAACGAT TTGAGTTCCA TCCTCGAAGG CAATGCCGGC  
301 ATCGACGCCG CCTACGATAT GCGCGGCGAA AGCATTITTCC TCGCGGGCTT  
351 TCAAGCCGAC GCATCTGATA TTTACCGCGA CGGCGTACGC GAAAGCGGGC  
401 AGGTGCGCCG TAGCACC GCC AACATCGAGC GCGTGGAAT CCTGAAAGGT  
451 CCGTCCTCCG TGCTTTATGG GCGTACCAAC GCGGGCGGTG TCATCAACAT  
501 GGTCAGCAAA TACGCCAACT TCAAACAAAG CCGTAATATC GGTACGGTTT

551 ATGGTTCGTG GGC~~AA~~ACCGT AGCCTGAATA TGGACATCAA CGAAGTGCTG

601 AACAAAAACG TCGCCATCCG TCTCACCGGC GAAGTCGGGC GCGCCAATTC

651 GTTCCGCAGC GGCATAGACA GCAAAAATGT CATGGTTTCG CCCAGCATTA

701 CCGTCAAAC~~T~~ CGACAACGGC TTGAAGTGG~~A~~ CGGGGCAATA CACCTACGAC

751 AATGTGGAGC GCACGCCCGA CCGCAGTCCG ACCAAGTCCG TGTACGACCG

801 CTTCGGACTG CTTACCGCA TGGGGTTCGC CCACCGGAAC GATTTTGTC~~A~~

851 AAGACAAGCT GCAAGTTTGG CGTTCCGACC TTGAATACGC CTTCAACGAC

901 AAATGGCGTG CCAATGGCA GCTCGCC~~CA~~ CGCACGGCGG CGCAGGATTT

951 TGATCATTTT~~C~~ TATGCAGGCA GCGAAAATGG CAACTTAATC AAACGTAACT

1001 ACGCCTGGCA GCAGACCGAC AACAAAACCC TGTCGTCAA CTTAACGCTC

1051 AACGGCGACT ACACCATCGG CCGTTTTGAA AACCACCTGA CCGTAGGCAT

1101 GGATTACAGC CGCGAACACC GCAACCCGAC ATTGGGTTTC AGCAGCGCCT

1151 TTTCCGCCTC CATCAACCCC TACGACCGCG CAAGCTGGCC GGCTTCGGGC

1201 AGATTGCAGC CTATTCTGAC CAAAACCGC CACAAAGCCG ACTCCTACGG

1251 CATCTTTGTG CAAACATCT TCTCCGCCAC GCCCGATTG AAATTCGTCC

1301 TCGGCGGCCG TTACGACAAA TACACCTTTA ATTCCGAAAA CAAACTCACC

1351 GGCAGCAGCC GCCAATACAG CGGACACTCG TTCAGCCCCA ACATCGGCGC

1401 AGTGTGGAAC ATCAATCCCG TCCACACACT TTACGCCTCG TATAACAAAG

1451 GCTTCGCGCC TTATGGCGGA CGCGGCGGCT ATTTGAGCAT CGATACGTTG

1501 TCTTCCGCCG TGTTC AACGC CGACCCGAG TACACCCGCC AATACGAAAC

1551 CGGCGTGAAA AGCAGTTGGC TGGACGACCG CCTCAGCACT ACGTTGTCTG

1601 CCTACCAAAT CGAACGCTTC AATATCCGCT ACCGCCCCGA TCCAAAAAAC

1651 AACCCTTATA TTTATGCGGT TAGCGGCAAA CACCGTTCGC GCGGCGTGGA

1701 ATTGTCCGCC ATCGGGCAAA TCATCCCCAA AAAA ACTCTA TCTGCGCGGT

1751 TCGTTGGGCG TGATGCAGGC GAAAGTCGTT GAAGACAAAG AAAATCCCGA  
1801 CCGAGTGGGC ATCCATTGGA ATAACACCAG CAACGTTACC GGCAACCTGT  
1851 TTTTCCGTGA TACCCCGACC GAAAACCTCT ACGGCGAAAT CGGCGTAACC  
1901 GGTACAGGCA AACGCTACGG TTACGACTCA AGAAATAAAG AAGTGACTAC  
1951 GCTTCCAGGC TTTGCCCAGAG TTGATGCCAT GCTTGGCTGG AACCATAAAA  
2001 ATGTTAACGT TACCTTTGCC GCAGCCAATC TGTTCATCA AAAATATTGG  
2051 CGTTCGGACT CTATGCCGGG TAATCCGCGC GGCTATACTG CCCGGGTAAA  
2101 TTACCGTTTC TGA

FIGURE 24A (suite 3)

## FIGURE 24B

1 MQIPFHLALL PTLIASFPV AAADTQDNGE HYTATLPTVS VVGQSOTSVL  
51 KGYINYDEAA VTRNGQLIKE TPQTIDTLNI QKNKNYGTND LSSILEGNAG  
101 IDAAYDMRGE SIFLRGFQAD ASDIYRDGVR ESGQVRRSTA NIERVEILKG  
151 PSSVLYGRTN GGGVINMVS K YANFKQSRNI GTVYGSWANR SLNMDINEVL  
201 NKNVAIRLTG EVGRANSFRS GIDSKNVMVS PSITVKLDNG LKWTGQYTYD  
251 NVERTPDORSP TKSVDYDRFGL PYRMGFAHRN DFKVDKLQVW RSOLEYAFND  
301 KWRAQWQLAH RTAAQDFDHF YAGSENGNLI KRNYAWQQTD NKTLSNLT  
351 NGDYTIGRFE NHLTVGMDYS REHRNPTLGF SSAFSASINP YDRASWPASG  
401 RLQPILTQNR HKADSYGIFV QNIFSATPDL KVLGGRYDK YTFNSENKLT  
451 GSSRQYSGHS FSPNIGAVWN INPVHTLYAS YNKGFPYGG RGGYLSIDTL  
501 SSAVFNADPE YTRQYETGVK SSWLDDRLST TLSAYQIERF NIRYRDPKN

551 NPYIYAVSGK HRSRGVELSA IGQIIPKKTL SARFVGRDAG ESR\*RQRKSR

601 PSGHPFE\*HQ QRYRQPVFPL YPDRKPLRRN RRNRYRQTLR LRLKK\*RS DY

651 ASRLCPS\*CH AWLEP\*KC\*R YLCRSQSVQS KILAFGLYAG \*SARLYCPGK

701 LPFL

FIGURE 24B (suite)

FIGURE 25A

1 ATGAAAATAT CATTTTCATT AGCTTTATTA CCCACGCTGA TTATTGCTTC  
51 CTTCCCTGTT GCTGCCGCCG ATACGCAGGA CAATGGTGAA CATTACACCG  
101 CCACTCTGCC CACCGTTTCC GTGGTCGGAC AGTCCGACAC CAGCGTACTC  
151 AAAGGTACA TCAACTACGA CGAAGCCGCC GTTACCCGCA ACGGACAGCT  
201 CATCAAAGAA ACGCCGCAAA CCATCGATAC GCTCAATATC CAGAAAAACA  
251 AAAATTACGG TACGAACGAT TTGAGTTCCA TCCTCGAAGG CAATGCCGGC  
301 ATCGACGCTG CCTACGATAT GCGCGGCGAA AGCATTTTCC TCGCGGTTT  
351 TCAAGCCGAC GCATCCGATA TTTACCGCGA CGGCGTGCGC GAAAGCGGAC  
401 AAGTGCGCCG CAGTACTGCC AACATCGAGC GCGTGAAAT CCTGAAAGGC  
451 CCGTCTTCG TGCTTTACGG CCGCACCAAC GCGCGCGGCG TCATCAACAT  
501 GGTGAGCAAA TACGCCAACT TCAAACAAAG CCGCAACATC GGTGCGGTTT



551 ACGGTTCTGTG GCGAAACCGC AGCCTGAATA TGGACATTAA CGAAGTGTTG

601 AACAAAAACG TCGCCATCCG TCTACCGGC GAAGTCGGGC GCGCCAATTC

651 GTTCCGCAGC GGCATAGACA GCAAAAATGT CATGGTTTCG CCCAGCATTAA

701 CCGTCAAACCT CGACAACGGC TTGAAGTGGA CGGGGCAATA CACCTACGAC

751 AATGTGGAGC GCAAGCCCGA CCGCAGTCCG ACCAAGTCCG TGTACGACCG

801 CTTCCGACTG CCTTACCGCA TGGGGTTCGC CCACCGGAAC GATTTTGCTA

851 AAGACAAGCT GCAAGTTTGG CGCTCCGACC TTGAATACGC CTCAACGAC

901 AAATGGCGTG CCCAATGGCA GCTCGCCAC CGCACGGCGG CGCAGGATTT

951 TGATCATTTT TATGCAGGCA GCGAAAATGG CAACTTAATC AAACGTAAC

1001 ACGCCTGGCA GCAGACCGAC AACAAAACCC TGTCGTCAA TTTACGCTA

1051 AACGGCGACT ACACCATCGG CCGTTTTGAA AACCATTGA CCGTAGGCAT

1101 GGATTACAGC CGCGAACACC GCAACCCGAC CTTAGGTTAC AGCCGCGCCT

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1151 T TACTGCTTC CATCGATCCA TACGACCGAG CAAGCTGGCC GGCTTCGGGC

1201 AGATTGCAGC CTATCCTCAC CCAAAACCGC CACAAAGCCG ACTCCTACGG

1251 CATCTTTGTG CAAAACATCT TCTCCGCCAC GCCCGATTTG AAATTCGTCC

1301 TCGGCGGTCTG TTACGACAAA TACACCTTTA ATTCCGAAAA CAAACTCACC

1351 GGCAGCAGCC GCCAATACAG CGGACACTCG TTCAGCCCCA ACATCGGCGC

1401 AGTGTGGAAC ATCAATCCCG TCCACACACT TTACGCCTCG TATAATAAAG

1451 GCTTCGCGCC TTATGGCGGA CGCGGCGGCT ATTTGAGCAT CAACACGTGC

1501 TCTTCGCGCG TGTTCACGC CGACCCCGAG TACACCCGCC AATACGAAAC

1551 CGGTGTGAAA AGCAGTTGGC TGGACGACCG CCTCAGCACT ACGTTGTCTG

1601 CCTACCAAAT CGAACGCTTC AATATCCGCT ACCGCCCCGA CGAGCAAAAT

1651 GATCCCTACA CTTGGGCAGT CGGCGGCAAA CACCGTTCGC GCGGCGTGGA

1701 ATTGTCCGCC ATCGGGCAAA TCATCCCCAA AAAACTCTAT CTGCGCGGTT

FIGURE 25A (suite 2)

1751 CGTTGGGCGT GATGCAGGCG AAAGTCGTTG AAGACAAAGA AAATCCCGAC  
1801 CGAGTGGGCA TCCATTTGAA TAACACCAGC AACGTTACCG GCAACCTGTT  
1851 TTTCCGTTAT ACCCCGACCG AAAACCTCTA CGGCGAAATC GGC GTAACCG  
1901 GTACAGGCAA ACGCTACGGT TACAAC TCAA GAAATAAAGA AGTGACTACG  
1951 CTTCCAGGCT TTGCCCAGT TGATGCCATG CTTGGCTGGA ACCATAAAAA  
2001 TGTTAACATT ACCTTTGCCG CAGCCAATCT GCTCAATCAA AAATATTGGC  
2051 GTTCGGATGC CATGCCCGGC GCGCCGCGCA CTTATACGGC GCGGGTTAAT  
2101 TACAGTTTCT AA

FIGURE 25A (suite 3)

## FIGURE 25B

1 MKISFHLALL PTLIASFPV AAADTQNGE HYATLPTVS VVGQSDTSVL

51 KGYINYDEAA VTRNGQLIKE TPQTIDTLNI QKNKNYGTND LSSILEGNAG

101 IDAAYDMRGE SIFLRGFQAD ASDIYRDGVR ESGQVRRSTA NIERVEILKG

151 PSSVLYGRTN GGGVINMVSK YANFKQSRNI GAVYGSWANR SLNMDINEVL

201 NKNVAIRLTG EVGRANSFRS GIDSKNMVS PSITVKLDNG LKWTGQYTYD

251 NVERTPDRSP TKSVDYRFGI PYRMGFAHRN DFKDKLQVW RSDLEYAFND

301 KWRAQWQLAH RTAAQDFDHF YAGSENGNLI KRNYAWQQTD NKTLSNFTL

351 NGDYTIGRFE NHLTVGMDYS REHRNPTLGY SRAFTASIDP YDRASWPASG

401 RLQPILTQNR HKADSYGIFV QNIFSATPDL KVLGGRYDK YTFNSENKLT

451 GSSRQYSGHS FSPNIGAVWN INPVHTLYAS YNKGFPYGG RGGYLSINTS

501 SSAVFNADPE YTRQYETGVK SSWLDDRLST TLSAYQIERF NIRYRPDEQN

551 DPYTWAVGGK HSRGVVELSA IGQIIPKKLY LRGSLGVMQA KVVEDKENPD

601 RVGIHLNNTS NVTGNLFFRY TPTENLYGEI GVTGTGKRYG YNSRNKEVTT

651 LPGFARVDAM LGWNHKNVNI TFAAANLLNQ KYWRSDAMPG APRTYTARVN

701 YSF\*

FIGURE 25B (suite)

## FIGURE 26A

1 ATGAAAATAT CATTTCAATTT AGCTTTATTA CCCACGCTGA TTATTGCTTC  
51 CTTCCTGTT GCTGCCGCCG ATACGCAGGA CAATGGTGAA CATTACACCG  
101 CCACTCTGCC CACCGTTTCC GTGGTCGGAC AGTCCGACAC CAGCGTACTC  
151 AAAGGCTACA TCAACTACGA CGAAGCCGCC GTTACCCGCA ACGGACAGCT  
201 CATCAAAGAA ACGCCGCAAA CCATCGATAC GCTCAATATC CAGAAAAACA  
251 AAAATTACGG TACGAACGAT TTGAGTTCCA TCCTCGAAGG CAATGCCGGC  
301 ATCGACGCTG CCTACGATAT GCGCGGTGAA AGCATTTTCC TCGCGGTTTT  
351 TCAAGCCGAC GCATCCGATA TTTACCGCGA CGGCGTGCGC GAAAGCGGAC  
401 AAGTGCGCCG CAGTACTGCC AACATCGAGC GCGTGAAAT CCTGAAAGGC  
451 CCGTCTTCG TGCTTTACGG CCGCACCAAC GCGGCGGCGC TCATCAACAT  
501 GGTCAGCAAA TACGCCAACT TCAAACAAAG CCGCAACATC GGAGCGGTTT

551 ACGGCTCATG GGC A ACCGC AGCCTGAATA TGGACATTAA CGAAGTGCTG

601 AACAAAAACG TCGCCATCCG TCTACCCGGC GAAGTCGGGC GCGCCAATTC

651 GTTCCGCAGC GGCATAGACA GCAAAAATGT CATGGTTTCG CCCAGCATTA

701 CCGTCAAACCT CGACAACGGC TTGAAGTGGA CGGGGCAATA CACCTACGAC

751 AATGTGGAGC GCACGCCCGA CCGCAGTCCG ACCAAGTCCG TGTACGACCG

801 CTTGGGACTG CCTTACCGCA TGGGGTTCGC CCACCGGAAC GATTTTGTCA

851 AAGACAAGCT GCAAGTTTGG CGTTCGACC TTGAATACGC CTTCAACGAC

901 AAATGGCGTG CCAATGGCA GCTCGCCAC CGCACGGCGG CGCAGGATTT

951 TGATCATTTT TATGCAGGCA GCGAAAATGG CAACTTAATC AAACGTAATC

1001 ACGCCTGGCA GCAGACCGAC AACAAAACCC TGTCGTCCAA CTTAACGCTC

1051 AACGGCGACT ACACCATCGG CCGTTTTGAA AACCACCTGA CCGTAGGCAT

1101 GGATTACAGC CGCGAACACC GCAACCCGAC ATTGGGTTTC AGCAGCGCCT

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1151 TTTCCGCCTC CATCAACCCC TACGACCGCG CAAGCTGGCC GGCTTCGGGC

1201 AGATTGCAGC CTATTCTGAC CCAAACCGC CACAAAGCCG ACTCCTACGG

1251 CATCTTTGTG CAAACATCT TCTCCGCCAC GCCCGATTTC AAATTCGTCC

1301 TCGGCGGCCG TTACGACAAA TACACCTTTA ATTCCGAAAA CAAACTCACC

1351 GGCAGCAGCC GCCAATACAG CGGACACTCG TTCAGCCCCA ACATCGGCGC

1401 AGTGTGGAAC ATCAATCCCG TCCACACACT TTACGCCTCG TATAACAAAG

1451 GCTTCGCGCC TTATGGCGGA CGCGGCGGCT ATTTGAGCAT CGATACGTTG

1501 TCTTCGCGCG TGTTCAACGC CGACCCCGAG TACACCGCC AATACGAAAC

1551 CGGCGTGAAA AGCAGTTGGC TGGACGACCG CCTCAGCACT ACGTTGTCTG

1601 CCTACCAAAAT CGAACGCTTC AATATCCGCT ACCGCCCCGA TCAAAAAAAC

1651 AACCTTATA TTTATGCGGT TAGCGGCAAA CACCGTTCGC GCGGCGTGGA

1701 ATTGTCCGCC ATCGGGCAAA TCATCCCCAA AAAACTCTAT CTGCGCGGTT

FIGURE 26-A (suite 2)



1751 CGTTGGGCGT GATGCAGGCG AAAGTCGTTG AAGACAAAGA AAATCCCGAC  
1801 CGAGTGGGCA TCCATTTGAA TAATACCAGC AACGTTACCG GCAACCTGTT  
1851 TTTCCGTTAT ACCCCGACCG AAAACCTCTA CGGCGAAATC GGC GTAACCG  
1901 GTACAGGCAA ACGCTACGGT TACAACTCAA GAAATAAAGA AGTGACTACG  
1951 CTTCCAGGCT TTGCCCGAGT TGATGCCATG CTTGGCTGGA ACCATAAAAA  
2001 TGTTAACGTT ACCTTTGCCG CAGCCAATCT GCTCAATCAA AAATATTGGC  
2051 GTTCGGACTC TATGCCGGGT AATCCGCGCG GCTATACTGC CCGGGTAAAT  
2101 TACCGTTTCT GA

FIGURE 26A (suite 3)

## FIGURE 26B

1 MKISFHLALL PTLIASFPV AAADTQDNGE HYTATLPTVS VVGQSDTSVL  
-----  
51 KGYINYDEAA VTRNGQLIKE TPQTIDTLNI QKNKNYGTND LSSILEGNAG  
  
101 IDAAYDMRGE SIFLRGFQAD ASDIYRDGVR ESGQVRRSTA NERVEILKG  
  
151 PSSVLYGRTN GGGVINMVSK YANFKQSRNI GAVYGSWANR SLNMDINEVL  
  
201 NKNVAIRLTG EVGRANSFRS GIDSKNVMVS PSITVKLONG LKWTGQYTYD  
  
251 NVERTPDRSP TKSVDYRFG L PYRMGFAHRN DFKDKLQVW RSOLEYAFND  
  
301 KWRAQWQLAH RTAAQDFDHF YAGSENGNLI KRNYAWQQTD NKTLSNLTL  
  
351 NGDYTIGRFE NHLTVGMDYS REHRNPTLGF SSAFSASINP YDRASWPASG  
  
401 RLQPILTQNR HKADSYGIFV QNIFSATPDL KFLVGGRYDK YTFNSENKLT  
  
451 GSSRQYSGHS FSPNIGAVWN INPVHTLYAS YNKGAFAPYG RGGYLSIDTL  
  
501 SSAVFNAOPE YTRQYETGVK SSWLDDRLST TLSAYQIERF NIRYRPDPKN

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551 NPYIYAVSGK HRSRGVELSA IGQIIPKKLY LRGLGVMQA KVVEDKENPD

601 RVGIHLNNTS NVTGNLFFRY TPTENLYGEI GVTGTGKRYG YNSRNKEVTT

651 LPGFARVDAM LGWNHKNVNV TFAAANLLNQ KYWRSDSMPG NPRGYTARVN

701 YRF\*

FIGURE 26B (suite)

FIGURE 27A  
-----

1 MKRFTYTLSD GLCIEELKR SAKKNLILRP VNMQTVSINV PPFFQDHALA

51 NWLAANETIL RNTLAKMPVH PVSHPNLPEW IWYRGIKTKL DTHSQSHIRI

101 TSSEILLPRK ETAAQIDHLR RLLNERAREY LLPRLEKHAA ETGLTPAATD

151 LSNAKTFWGV CRPHTGIRLN WRLIGTPEYV ADYVCIELC HLRHPDHSR

201 FWHLVNTLTP HTDNAKSWLK AHGRELFVLG \*

## FIGURE 27B

1 ATGAAACGCT TCACCTATAC TCTTTCCGAC GGCTTGTGCA TCGAAATCGA  
51 ACTCAAACGC AGTGCCAAGA AAAATCTGAT TCTGCGCCCC GTCAATATGC  
101 AGACGGTCAG CATCAACGTC CCACCCTTTT TTCAAGACCA CGCGTTAGCA  
151 AACTGGCTGG CGGCAAACGA AACGATTTTG CGGAACACGC TTGCTAAAAT  
201 GCCCGTGCAT CCTGTTTCCC ACCCAAACCTT ACCCGAGTGG ATTTGGTATC  
251 GGGGAATAAA GACCAAGCTG GATACCCACA GCCAAAGCCA TATCCGTATC  
301 ACGTCGTCTG AAATCCTGCT TCCCCGAAAA GAAACCGCCG CACAAATCGA  
351 CCACCTGCGC CGCCTGTTGA ACGAACGCGC CCGCGAATAC CTGCTGCCCC  
401 GCCTTGAAAA ACACGCAGCC GAAACAGGAC TGACTCCCGC TGCCACAGAC  
451 CTGAGCAACG CCAAACCTT TTGGGGCGTA TGCCGCCCGC ACACCGGCAT  
501 CCGCCTCAAC TGGCGGCTGA TCGGCACGCC CGAATACGTC GCCGACTATG

551 TCTGCATCCA CGAACTCTGC CACCTCCGCC ACCCCGACCA CAGTCCGCGC

601 TTTTGGCATT TGGTGAACAC GCTGACGCCG CATACCGACA ATGCTAAAAG

651 TTGGCTGAAG GCGCACGGGC GGAATTGTT TGTGCTGGGG TAA

FIGURE 27B (suite)

## FIGURE 28A

1 ATGAGCAAGA TTATTGTGCT GACCGCAGGC CACAGCAACA CCGACCCGGG  
51 TCGGTCAAC GGAAGCGACC GTGAGGCGGA CTTGGCGCAG GATATGCGCA  
101 ACATTGTGGC TTCAATCCTG CGTAACGATT ACGGCCTGAC CGTTAAAACC  
151 GACGGCACGG GCAAAGGCAA TATGCCGCTG CGCGAAGCGG TCAAGCTGAT  
201 TCGCGGCTCG GATGTGGCGA TTGAGTTTCA CACCAACGCT GCCGTCAGCA  
251 AAGCGGCGAC AGGCATCGAA GCCTTGAGTA CCGTTAAAAA CAAACGCTGG  
301 TGTCAGGTGT TGAGCAAAGC CGTTGCCAAG AAAACCGGCT GGAAACTGCG  
351 CGGCGAAGAC GGCTTTAAAC CCGACAATGC GGGCCAGCAT TCGCGCCTGG  
401 CTTATGCACA AGCCGGCGGC ATTGTGTTTG AGCCTTTTTT CATCAGCAAC  
451 GACACTGATT TGGCCTTGTT TAAGACGACT AAATGGGGCA TCTGCCGCGC  
501 GATTGCGGAC GCGATTGCGA TGGAATTGGG GCGGCAAGA GTATGA

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FIGURE 28B

1 MSKIIVLTAG HSNTDPGAVN GSDREADLAQ DMRNIVASIL RNDYGLTVKT  
 51 DGTGKGNMPL REAVKLIRGS DVAIEFHTNA AVSKAATGIE ALSTVKNKRW  
 101 CQVLSKAVAK KTGWKLRGED GFKPDNAGQH SRLAYAQAGG IVFEPFFISN  
 151 DTDLALFKTT KWGICRAIAD AIAMELGAAR V\*



FIGURE 29A  
-----

1 ATGCGTATTT TGGATATTTT TAAAAACCCA GCGACAGGCA ATGTGTCGCA  
51 CTCGAAACTG TGGGCAAACG TTGCCTGCGC GCGGGGACG GTTAAGTTTG  
101 TGATGCTGCC CGACCCGTCG GCGGAGATTT GGGCGGTGTA TTTGGGCATT  
151 GTCGGCGGCT ATGCGGTGGC GCGTTCGTTG GTCAGCGTCA AACGTCAGGA  
201 GGTCGAGAAT GAATCTCGTG AAACGCTGG CGAATAA

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FIGURE 29B

1 MRILDIFKNP ATGNVSHSKL WANVACAAGT VKFVMLPPDS AEIWAVYLG

51 VGGYAVARSL VSVKRQEVEN ESRETAGE\*

FIGURE 30A  
-----

1 ATGCGGTGGC GCGTTCGTTG GTCAGCGTCA AACGTCAGGA GGTGCGAGAAT  
51 GAATCTCGTG AAAGTCTGCTGG CGAATAACTG GCAACCGATT GCCATCATCG  
101 CGCTTGTCGG CACGGGTTTG GCGGTGTCGC ACCATCAAGG CTACAAGTCG  
151 GCTTTTGC GA AGCAGCAGGC GGTCAATTGAG AAAATGAAGC GCGACAAGGC  
201 GCAAGCCCTG CTGTTGTCGG CTCAAAACTA CGCCCGCGAA CTGGAACAGG  
251 CGCGTGCGGA AGCTAAAAAA TATGAAGTCA AGGCGCACGC CGTCGGCATG  
301 GCTTTGCGGA AAAACAGGC GGAAGTCAGC CGTCTGAAAA CGGAAAATAA  
351 AAAGGAAATC GAAAATGTCC TTAAGTCAAGA CCGTA AAAAT GCAGGCGGCG  
401 GTTGTATTGA CGGCTTTGGC CATCACGGCT TGCAGCTCTA CAAGCGCGCC  
451 CTCGGCTACG GAAATTA

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FIGURE 30B  
-----

1 MRWRVRWSAS NVRRSRMNLV KLLANNWQPI AIIALVGTGL AVSHHQGYKS

51 AFAKQQAVIE KMKRDKAQAL LLSAQNYARE LEQARAEAKK YEVKAHAVGM

101 ALAKKQAEVS RLKTENKKEI ENVLTQDRKN AGGGCIDGFG HHGLQLYKRA

151 LGYGN\*

## FIGURE 31A

1 ATGTCCTTAC TCAAGACCGT AAAAATGCAG GCGGCGGTTG TATTGACGGC  
51 TTTGGCCATC ACGGCTTGCA GCTCTACAAG CGCGCCCTCG GCTACGGAAA  
101 TTAAGGTTGT CGAAAAGGCG GTCATGCCGA CACCGCCTGC CGCGTTGATG  
151 GTCGCGCCGG TCGCCCCGAA TCCGCCGAAA GACGGCAAGA CGGCCACGCT  
201 GTTGGAACAC GCCGCCGAGT TTGGCGGCTA TGTTGCCGAA CTTGAAAACC  
251 AAAATCAGGC TTGGCGCGAC TGGGCGGGCA ATCACTCCCG CAAAGTCGGA  
301 AACTGA

FIGURE 31B

1 MSLKTVKMQ AAVVLTALAI TACSSTSAPS ATEIKVVEKA VMPTPPAALM

51 VAPVRPNPPK DGKTATLLEH AAEFGGYVAE LENQNQAWRD WAGNHSRKVG

101 N\*

## FIGURE 32A

1 GTGCTGGCAG TTTTGCTTGC TGGTGTAGCC TTCGCCCTGA GCGATGATTT  
51 CATGGTTGGC TGCTTTCAAA CGCCAACGGT ATTCGCCTTT TCGTCTTTA  
101 TAGATTTCAA AATACATAAG GTTCTCCTA TGAATGAGTA CACGTTTTCT  
151 TACCGCTTTA ACGGCAAGTC CTGGTCATTG AGCATTTGGG CGGACAACCC  
201 TGAAGAAGCC AGGGCGAAAT TTCGGGCTGC ACGAGAAAAT GCGCACTATG  
251 ACGGCGAAGT TGTAGCAAAG GTTTATACAT TTGTAAATAT TTCGTGGGTT  
301 AAGAAATTGT ACAAGCGGAC AAAATATTTA ATGGGTATCA AAGAATGA

FIGURE 32B  
-----

1 VLAVLLAGVA FALSDDFMVG CFQTPTVFAF CVFIDFKIHK VSPMNEYTFS

51 YRFNGKSWSL SIWADNPEEA RAKFRAAREN AHYDGEVVAK VYTFVNISWV

101 KKLYKRTKYL MGIKE\*



## FIGURE 33A

1 ATGACATTGC TCAATCTAAT GATAATGCAA GATTACGGTA TTCCGTTTG  
51 CCTGACACTG ACGCCCTATT TGCAACATGA ACTATTTTCG GCTATGAAAT  
101 CCTATTTTTC CAAATATATC CTACCCGTTT CACTTTTAC CTTGCCACTA  
151 TCCCTTTCCC CATCCGTTTC GGCTTTTACG CTGCCTGAAG CATGGCGGGC  
201 GGCGCAGCAA CATTGCGCTG ATTTTCAAGC GTCCATTAC CAGCGTGATG  
251 CAGTGCGCGC ACGGCAACAA CAAGCCAAGG CCGCATTCTT TCCCATGTA  
301 TCGCCAATG CCAGCTACCA GCGCCAGCCG CCATCGATTT CTTCCACCCG  
351 CGAAACACAG GGATGGAGCG TGCAGGTGGG ACAAACCTTA TTTGACGCTG  
401 CCAAATTTGC ACAATACCGC CAAAGCAGGT TCGATACGCA GGCTGCAGAA  
451 CAGCGTTTCG ATGCGGCACG CGAAGAATTG CTGTTGAAAG TTGCCGAAAG  
501 TTATTTCAAC GTTTTACTCA GCCGAGACAC CGTTGCCGCC CATGCGGCGG

551 AAAAAGAGGC TATGCCAG CAGGTAAGGC AGGCGCAGGC TTTATTCAAT

601 AAAGGTGCTG CCACCGCGCT GGATATTCAC GAAGCCAAAG CCGGTTACGA

651 CAATGCCCTG GCCAAGAAA TCGCCGTATT GGCTGAGAAA CAAACCTATG

701 AAAACCAAGTT GAACGACTAC ACCGGCCTGG ACAGCAAACA AATCGAGGCC

751 ATAGATACCG CCAACCTGTT GGCACGCTAT CTGCCCAAAGC TGGAACGTTA

801 CAGTCTGGAT GAATGGCAGC GCATTGCCTT ATCCAACAAT CATGAATACC

851 GGATGCAGCA GCTTGCCCTG CAAAGCAGCG GACAGGCGCT TCGGGCAGCA

901 CAGAACAGCC GCTATCCAC CGTTTCTGCC CATGTCGGCT ATCAGAATAA

951 CCTCTACACT TCATCTGCGC AGAATAATGA CTACCACTAT CGGGGCAAAG

1001 GGATGAGCGT CGGCGTACAG TTGAATTTGC CGCTTTATAC CGGCGGAGAA

1051 TTGTCGGGCA AAATCCATGA AGCCGAAGCG CAATACGGGG CTGCCGAAGC

1101 ACAGCTGACC GCAACCGAGC GGCACATCAA ACTCGCCGTA CGCCAGGCTT

1151 ATACCGAAAG CGGTGCGGCG CGTTACCAA TCATGGCGCA AGAACGGTT

1201 TTGGAAGCA GCCGTTTGAA ACTGAAATCG ACCGAAACCG GCCAACAATA

1251 CGGCATCCGC AACCGGCTGG AAGTAATACG GGCGCGGCAG GAAGTCGCCC

1301 AAGCAGAACA GAAACTGGCT CAAGCACGGT ATAAATTCAT GCTGGCTTAT

1351 TTGCGCTTGG TGAAAGAGAG CGGGTTAGGG TTGGAAACGG TATTTGCGGA

1401 ATAA

FIGURE 33A (suite 2)

FIGURE 33B

1 MTLNLNMIQ DYGISVCLTL TPYLQHELFS AMKSYFSKYI LPVSLFTLPL

51 SLSPSVSAFT LPEAWRAAQ HSADFQASHY QRDAVRARQQ QAKAAFLPHV

101 SANASYQRQP PSISSTRETQ GWSVQVGQTL FDAAKFAQYR QSRFDTQAAE

151 QRFDAAREEL LLKVAESYFN VLLSRDTVAA HAAEKEAYA QVRQAQALFN

201 KGAATALDIH EAKAGYDNAL AQEIAVLAEK QTYENQLNDY TGLDSKQIEA

251 IDTANLLARY LPKLERYSLD EWQRIALSNN HEYRMQQLAL QSSGQALRAA

301 QNSRYPTVSA HVGYQNNLYT SSAQNNDYHY RGKGMSVGVQ LNLPLYTGGE

351 LSGKIHAEAE QYGAAEAQLT ATERHIKLAV RQAYTESGAA RYQIMAQERV

401 LESSRLKLKS TETGQQYGIR NRLEVIRARQ EVAQAEQKLA QARYKFMLAY

451 LRLVKESGLG LETVFAE\*



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551 AAAAAGAGGC TTATGCCAG CAGGTAAGGC AGGCGCAGGC TTTATTCAAT

601 AAAGGTGCTG CCACCGCGCT GGATATTCAC GAAGCCAAAG CCGGTTACGA

651 CAATGCCCTG GCCCAAGAAA TCGCCGTATT GGCTGAGAAA CAAACCTATG

701 AAAACCAAGT GAACGACTAC ACCGGCCTGG ACAGCAAACA AATCGAGGCC

751 ATAGATACCG CCAACCTGTT GGCACGCTAT CTGCCCAAGC TGGAACGTTA

801 CAGTCTGGAT GAATGGCAGC GCATTGCCTT ATCCAACAAT CATGAATACC

851 GGATGCAGCA GCTTGCCCTG CAAAGCAGCG GACAGGCGCT TCGGGCAGCA

901 CAGAACAGCC GCTATCCAC CGTTTCTGCC CATGTCGGCT ATCAGAATAA

951 CCTCTACACT TCATCTGCGC AGAATAATGA CTACCACTAT CGGGGCAAAG

1001 GGATGAGCGT CGGCGTACAG TTGAATTTGC CGCTTTATAC CGGCGGAGAA

1051 TTGTCGGGCA AAATCCATGA AGCCGAAGCG CAATACGGGG CTGCCGAAGC

1101 ACAGCTGACC GCAACCGAGC GGCACATCAA ACTCGCCGTA CGCCAGGCTT

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1151 ATACCGAAAG CGGTGCGGCG CGTTACCAA TCATGGCGCA AGAACGGGTT

1201 TTGGAAAGCA GCCGTTTGAA ACTGAAATCG ACCGAAACCG GCCAACATA

1251 CGGCATCCGC AACCGGCTGG AAGTAATACG GCGCGGCAG GAAGTCGCC

1301 AAGCAGAACA GAACTGGCT CAAGCACGGT ATAAATTCAT GCTGGCTTAT

1351 TTGCGCTTGG TGAAAGAGAG CGGGTTAGGG TTGGAAACGG TATTTGCGGA

1401 ATAA

FIGURE 34A (suite 2)

## FIGURE 34B

1 MTLNLNMIMQ DYGISVCLTL TPYLQHELFS AMKSYFSKYI LPVSLFTLPL

51 SLSPSVSAFT LPEAWRAAQQ HSADFQASHY QRDAVRARQQ QAKAAFLPHV

101 SANASYQRQP PSISSTRETQ GWSVQVGQTL FDAAKFAQYR QSRFDTQAAE

151 QRFDAAREEL LLKVAESYFN VLLSRDTVAA HAAEKEAYAQ QVRQAQALFN

201 KGAATALDIH EAKAGYDNAL AQEIAVLAEK QTYENQLNDY TGLDSKQIEA

251 IDTANLLARY LPKLERYSLD EWQRIALSNN HEYRMQQLAL QSSGQALRAA

301 QNSRYPTVSA HVGYNLNYT SSAQNNDYHY RGKGMSVGVQ LNLPLYTGGE

351 LSGKIHEAEA QYGAAEAQLT ATERHIKLAV RQAYTESGAA RYQIMAQERV

401 LESSRLKLKS TETGQQYGIR NRLEVIRARQ EVAQAEQKLA QARYKFMLAY

451 LRLVKESGLG LETVFAE\*



## FIGURE 35A

1 ATGACATTGC TCAATCTAAT ATGCAAGATT ACGGTATTTTC CGTTTGCCTG

51 ACACTGACGC CCTATTTGCA ACATGAACTA TTTTCGGCTA TGAAATCCTA

101 TTTTCCAAA TATATCCTAC CCGTTTCACT TTTTACCTTG CCACTATCCC

151 TTTCCCATC CGTTTCGGCT TTTACGCTGC CTGAAGCATG GCGGGCGGCG

201 CAGCAACATT CGGCTGATTT TCAAGCGTCC CATTACCAGC GTGATGCAGT

251 GCGCGCACGG CAACAACAAG CCAAGGCCGC ATTCCTTCCC CATGTATCCG

301 CCAATGCCAG CTACCAGCGC CAGCCGCCAT CGATTTCTTC CACCCGCGAA

351 ACACAGGGAT GGAGCGTGCA GGTGGGACAA ACCTTATTG ACTCTGCCAA

401 ATTTGCACAA TACCGCCAAA GCAGGTTCTGA TACGCAGGCT GCAGAACAGC

451 GTTTCGATGC GGCACGCGAA GAATTGCTGT TGAAAGTTGC CGAAAGTTAT

501 TTCAACGTTT TACTCAGCCG AGACACCGTT GCCGCCCATG CGGCGGAAAA

1101 CTGACCGCAA CCGAGCGGCA CATCAAATC GCCGTACGCC AGGCTTATAC

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1151 CGAAAGCGGT GCGGCGCGTT ACCAAATCAT GCGCAAGAA CGGGTTTTGG

1201 AAAGCAGCCG TTTGAACTG AAATCGACCG AAACCGGCCA ACAATACGGC

1251 ATCCGCAACC GGCTGGAAGT AATACGGGCG CGGCAGGAAG TCGCCCAAGC

1301 AGAACAGAAA CTGGCTCAAG CACGGTATAA ATTCATGCTG GCTTATTTGC

1351 GCTTGGTGAA AGAGAGCGGG TTAGGGTTGG AAACGGTATT TGCGGAATAA

FIGURE 35A (suite 2)

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FIGURE 35B

1 MTLNLICKI TVFPFA\*H\*R PICNMNYFRL \*NPIFPNISI PFHFLPCHYP  
 51 FPHPFRLRLC LKHGGRRSNI RLIFKRPITS VMQCAHGNNK PRPHSFPMPY  
 101 PMPATSASRH RFLPPAKHRD GACRWDPKPYL TLPNLHNTAK AGSIRRLQNS  
 151 VSMRHAKNCC \*KLPKVISTF YSAETPLPPM RRKKRLMPSR \*GRRRLYSIK  
 201 VLPPR\*IFTK PKPVTTMPWP KKSPYWLNRK PMKTS\*TTTP AWTANKSRP\*  
 251 IPPTCWAHAIC PSWNVTVWMN GSALPYPTIM NTGCSLPCCK AADRRFGQHR  
 301 TAAIPPFLPM SAIRITSTLH LRRIMTTTIG AKG\*ASAYS\* ICRFIPAENC  
 351 RAKSMKPKRN TGLPKHS\*PQ PSGTSNSPYA RLIPKAVRRV TKS WRKNGFW  
 401 KAAV\*N\*NRP KPANNTASAT GWK\*YGRGRK SPKQNRNWLK HGINSCLWIC  
 451 AW\*KRAG\*GW KRYLRN

## FIGURE 36A

1 ATGACATTGC TCAATCTAAT GATAATGCAA GATTACGGTA TTTCCGTTTG  
51 CCTGACACTG ACGCCCTATT TGCAACATGA ACTATTTTCG GCTATGAAAT  
101 CCTATTTTTC CAAATATATC CTACCCGTTT CACTTTTTAC CTTGCCACTA  
151 TCCCTTTCCC CATCCGTTTC GGCTTTTACG CTGCCTGAAG CATGGCGGGC  
201 GCGCGAGCAA CATTGCGCTG ATTTTCAAGC GTCCCATAC CAGCGTGATG  
251 CAGTGCGCGC ACGGCAACAA CAAGCCAAGG CCGCATTCTT TCCCCATGTA  
301 TCCGCCAATG CCAGCTACCA GCGCCAGCCG CCATCGATTT CTTCCACCCG  
351 CGAAACACAG GGATGGAGCG TGCAGGTGGG ACAAACCTTA TTTGACGCTG  
401 CCAAATTTGC ACAATACCGC CAAAGCAGGT TCGATACGCA GGCTGCAGAA  
451 CAGCGTTTCG ATGCGGCACG CGAAGAATTG CTGTTGAAAG TTGCCGAAAG  
501 TTATTTCAAC GTTTTACTCA GCCGAGACAC CGTTGCCGCC CATGCGGCGG

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551 AAAAAGAGGC TTATGCCAG CAGGTAAGGC AGGCGCAGGC TTTATTCAAT

601 AAAGGTGCTG CCACGCGCT GGATATTCAC GAAGCCAAAG CCGTTACGA

651 CAATGCCCTG GCCCAAGAAA TCGCCGTATT GGCTGAGAAA CAAACCTATG

701 AAAACCAAGT GAACGACTAC ACCGACCTGG ATAGCAAACA AATCGAGGCC

751 ATAGATACCG CCAACCTGTT GGCACGCTAT CTGCCAAGC TGGAACGTTA

801 CAGTCTGGAT GAATGGCAGC GCATTGCCTT ATCCAACAAT CATGAATACC

851 GGATGCAGCA GCTTGCCCTG CAAAGCAGCG GACAGGCGCT TCGGCGAGCA

901 CAGAACAGCC GCTATCCAC CGTTTCTGCC CATGTCGGCT ATCAGAATAA

951 CCTCTAACT TCATCTGCGC AGAATAATGA CTACCACTAT CGGGGCAAAG

1001 GGATGAGCGT CGGCGTACAG TTGAATTTGC CGCTTTATAC CGGCGGAGAA

1051 TTGTCGGGCA AAATCCATGA AGCCGAAGCG CAATACGGGG CCGCCGAAGC

1101 ACAGCTGACC GCAACCGAGC GGCACATCAA ACTCGCCGTA CGCCAGGCTT

1151 ATACCGAAAG CGGTGCGGCG CGTTACCAAA TCATGGCGCA AGAACGGGTT

1201 TTGGAAAGCA GCCGTTTGAA ACTGAAATCG ACCGAAACCG GCCAACAATA

1251 CGGCATCCGC AACCGGCTGG AAGTAATACG GGC GCGGCAG GAAGTCGCC

1301 AAGCAGAACA GAACTGGCT CAAGCACGGT ATAAATTCAT GCTGGCTTAT

1351 TTGCGCTTGG TGAAAGAGAG CGGGTTAGGG TTGGAAACGG TATTTGCGGA

1401 ATAA

FIGURE 36A (suite 2)

FIGURE 36B

1 MTLNLNLMIMQ DYGISVCLTL TPYLQHELFS AMKSYFSKYI LPVSLFTLPL  
51 SLSPSVSAFT LPEAWRAAQQ HSADFQASHY QRDAVRARQQ QAKAAFLPHV  
101 SANASYQRQP PSISSTRETQ GWSVQVQQL FDAAKFAQYR QSRFDTQAAE  
151 QRFDAAREEL LLKVAESYFN VLLSRDTVAA HAAEKEAYA QVRQAQALFN  
201 KGAATALDIH EAKAGYDNAL AQEI AVLAEK QTYENQLNDY TOLDSKQIEA  
251 IDTANLLARY LPKLERYS LD EWQRIALSNN HEYRMQQLAL QSSGQALRAA  
301 QNSRYPTVSA HVG YQNNLYT SSAQNNDYHY RGKMSVGVQ LNLPLYTGGE  
351 LSGKIHEAEA QYGAAEAQLT ATERHIKLAV RQAYTESGAA RYQIMAQERV  
401 LESSRLKLKS TETGQQYGIR NRLEVIRARQ EVAQAEQKLA QARYKFMLAY  
451 LRLVKESGLG LETVFAE\*



## FIGURE 37A

1 ATGACATTGC TCAATCTAAT GATAATGCAA GATTACGGTA TTTCCGTTTG  
51 CCTGACACTG ACGCCCTATT TGCAACATGA ACTATTTTCG GCTATGAAAT  
101 CCTATTTTTC CAAATATATC CTACCCGTTT CACTTTTTAC CTTGCCACTA  
151 TCCCTTTCCC CATCCGTTTC GGCTTTTACG CTGCCTGAAG CATGGCGGGC  
201 GGC GCAGCAA CATTGCGCTG ATTTTCAAGC GTCCCATAC CAGCGTGATG  
251 CAGTGC GCGC ACGGCAACAA CAAGCCAAGG CCGCATTCCT TCCCCATGTA  
301 TCCGCCAATG CCAGCTACCA GCGCCAGCCG CCATCGATTT CTTCCACCCG  
351 CGAAACACAG GGATGGAGCG TGCAGGTGGG ACAAACCTTA TTTGACGCTG  
401 CCAAATTTGC ACAATACCGC CAAAGCAGGT TCGATACGCA GGCTGCAGAA  
451 CAGCGTTTCG ATGCGGCACG CGAAGAATTG CTGTTGAAAG TTGCCGAAAG  
501 TTATTTCAAC GTTTTACTCA GCCGAGACAC CGTTGCCGCC CATGCGGCGG

551 AAAAAGAGGC TTATGCCAG CAGGTAAGGC AGGCGCAGGC TTTATTCAAT

601 AAAGGTGCTG CCACGCGCT GGATATTCAC GAAGCCAAAG CCGGTTACGA

651 CAATGCCCTG GCCCAAGAAA TCGCCGTATT GGCTGAGAAA CAAACCTATG

701 AAAACCAGTT GAACGACTAC ACCGACCTGG ATAGCAAACA AATCGAGGCC

751 ATAGATACCG CCAACCTGTT GGCACGCTAT CTGCCCAAGC TGGAACGTTA

801 CAGTCTGGAT GAATGGCAGC GCATTGCCTT ATCCAACAAT CATGAATACC

851 GGATGCAGCA GCTTGCCCTG CAAAGCAGCG GACAGGCGCT TCGGGCAGCA

901 CAGAACAGCC GCTATCCAC CGTTTCTGCC CATGTGGGCT ATCAGAATAA

951 CCTCTACACT TCATCTGCGC AGAATAATGA CTACCACTAT CGGGGCAAAG

1001 GGATGAGCGT CGGCGTACAG TTGAATTTGC CGCTTTATAC CGGCGGAGAA

1051 TTGTCGGGCA AAATCCATGA AGCCGAAGCG CAATACGGGG CCGCCGAAGC

1101 ACAGCTGACC GCAACCGAGC GGCACATCAA ACTCGCCGTA CGCCAGGCTT

FIGURE 3A (suite 1)

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1151 ATACCGAAAG CGGTGCGGCG CGTTACCAA TCATGGCGCA AGAACGGGTT

1201 TTGGAAAGCA GCCGTTTGAA ACTGAAATCG ACCGAAACCG GCCAACAATA

1251 CGGCATCCGC AACCGGCTGG AAGTAATACG GCGCGGCAG GAAGTCGCCC

1301 AAGCAGAACA GAACTGGCT CAAGCACGGT ATAAATTCAT GCTGGCTTAT

1351 TTGCGCTTGG TGAAAGAGAG CGGGTTAGGG TTGGAAACGG TATTTGCGGA

1401 ATAA

FIGURE 37A (suite 2)

## FIGURE 37B

1 MTLNLMMIMQ DYGISVCLTL TPYLQHELFS AMKSYFSKYI LPVSLFTLPL

51 SLSPSVSAFT LPEAWRAAQQ HSADFQASHY QRDAVRARQQ QAKAAFLPHV

101 SANASYQRQP PSISSTRETQ GWSVQVGQTL FDAAXFAQYR QSRFDTQAAE

151 QRFDAAREEL LLKVAESYFN VLLSRDTVAA HAAEKEAYAQ QVRQAQALFN

201 KGAATALDIH EAKAGYDNAL AQEIAVLAEK QTYENQLNDY TDLSKQIEA

251 IDTANLLARY LPKLERYSLD EWQRIALSNH HEYRMQQLAL QSSGQALRAA

301 QNSRYPTVSA HVGYNQNNLYT SSAQNNDYHY RGKGM SVGVQ LNLPLYTGGE

351 LSGKIHAEA QYGAAEAQLT ATERHIKLA V RQAYTESGAA RYQIMAQERV

401 LESSRLKLKS TETGQQYGIR NRLEVIRARQ EVAQAEQKLA QARYKFMLAY

451 LRLVKESGLG LETVFAE\*

FIGURE 38A

1 ATGACATTGC TCAATCTAAT GATAATGCAA GATTACGGTA TTTCCGTTTG  
51 CCTGACACTG ACGCCCTATT TGCAACATGA ACTATTTTCG GCTATGAAAT  
101 CCTATTTTTC CAAATATATC CTACCCGTTT CACTTTTTAC CTTGCCACTA  
151 TCCCTTTCCC CATCCGTTTC GGCTTTTACG CTGCCTGAAG CATGGCGGGC  
201 GCGCGAGCAA CATTGGGCTG ATTTTCAAGC GTCCATTAC CAGCGTGATG  
251 CAGTGCGCGC ACGGCAACAA CAAGCCAAGG CCGCATTCTT TCCCCATGTA  
301 TCCGCCAATG CCAGCTACCA GCGCCAGCCG CCATCGATTT CTTCCACCCG  
351 CGAAACACAG GGATGGAGCG TGCAGGTGGG ACAAACCTTA TTTGACGCTG  
401 CCAAATTTGC ACAATACCGC CAAAGCAGGT TCGATACGCA GGCTGCAGAA  
451 CAGCGTTTCG ATGCGGCACG CGAAGAATTG CTGTTGAAAG TTGCCGAAAG  
501 TTATTTCAAC GTTTTACTCA GCCGAGACAC CGTTGCCGCC CATGCGGCGG

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551 AAAAAGAGGC TTATGCCCAG CAGGTAAGGC AGGCGCAGGC TTTATTCAAT

601 AAAGGTGCTG CCACCGCGCT GGATATTCAC GAAGCCAAAAG CCGGTTACGA

651 CAATGCCCTG GCCCAAGAAA TCGCCGTATT GGCTGAGAAA CAAACCTATG

701 AAAACCAGTT GAACGACTAC ACCGACCTGG ATAGCAAACA AATCGAGGCC

751 ATAGATACCG CCAACCTGTT GGCACGCTAT CTGCCCAAGC TGGAACGTTA

801 CAGTCTGGAT GAATGCGAGC GCATTGCCTT ATCCAACAAT CATGAATACC

851 GGATGCAGCA GCTTGCCCTG CAAAGCAGCG GACAGGCGCT TCGGGCAGCA

901 CAGAACAGCC GCTATCCCAC CGTTTCTGCC CATGTGCGCT ATCAGAATAA

951 CCTCTACACT TCATCTGCGC AGAATAATGA CTACCACTAT CGGGGCAAAG

1001 GGATGAGCGT CGGCGTACAG TTGAATTTGC CGCTTTATAC CGGCGGAGAA

1051 TTGTCGGGCA AAATCCATGA AGCCGAAGCG CAATACGGGG CCGCCGAAGC

1101 ACAGCTGACC GCAACCGAGC GGCACATCAA ACTCGCCGTA CGCCAGGCTT

FIGURE 38A (suite 1)

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1151 ATACCGAAAG CGGTGCGGCG CGTTACCAA TCATGGCGCA AGAACGGGTT

1201 TTGGAAAGCA GCCGTTTGAA ACTGAAATCG ACCGAAACCG GCCAACAATA

1251 CGGCATCCGC AACCGGCTGG AAGTAATACG GCGCGGCAG GAAGTCGCCC

1301 AAGCAGAACA GAAACTGGCT CAAGCACGGT ATAAATTCAT GCTGGCTTAT

1351 TTGCGCTTGG TGAAAGAGAG CGGGTTAGGG TTGGAAACGG TATTTGCGGA

1401 ATAA

FIGURE 38A (suite 2)

## FIGURE 38B

1 MTLNLNMIMQ DYGISVCLTL TPYLQHELFS AMKSYFSKYI LPVSLFTLPL

51 SLSPSVSAFT LPEAWRAAQQ HSADFQASHY QRDAVRARQQ QAKAAFLPHV

101 SANASYQRQP PSISSTRETQ GWSVQVGQTL FDAAKFAQYR QSRFDTQAAE

151 QRFDAAREEL LLKVAESYFN VLLSRDTVAA HAAEKEAYA QVRQAQALFN

201 KGAATALDIH EAKAGYDNAL AQEIAVLAEK QTYENQLNDY TOLDSKQIEA

251 IDTANLLARY LPKLERYSLD EWQRIALSNN HEYRMQQLAL QSSGQALRAA

301 QNSRYPTVSA HVGYNQNNLYT SSAQNNDYHY RGKGMSVG VQ LNLPLYTGGE

351 LSGKIHEAEA QYGAAEAQLT ATERHIKLAV RQAYTESGAA RYQIMAQERV

401 LESSRLKLKS TETGQQYGIR NRLEVIRARQ EVAQAEQKLA QARYKFMLAY

451 LRLVKESGLG LETVFAE\*



FIGURE 39A

1 ATGACATTGC TCAATCTAAT GATAATGCAA GATTACGGTA TTTCCGTTTG  
51 CCTGACACTG ACGCCCTATT TGCAACATGA ACTATTTTCG GCTATGAAAT  
101 CCTATTTTTC CAAATATATC CTACCCGTTT CACTTTTAC CTTGCCACTA  
151 TCCCTTTCCC CATCCGTTTC GGCTTTTACG CTGCCTGAAG CATGCGGGC  
201 GCGCGAGCAA CATTGCGCTG ATTTTCAAGC GTCCATTAC CAGCGTGATG  
251 CAGTGCGCGC ACGGCAACAA CAAGCCAAGG CCGCATTCTT TCCCCATGTA  
301 TCCGCCAATG CCAGCTACCA GCGCCAGCCG CCATCGATTT CTTCACCCG  
351 CGAAACACAG GGATGGAGCG TGCAGGTGGG ACAAACCTTA TTTGACGCTG  
401 CCAAATTTGC ACAATACCGC CAAAGCAGGT TCGATACGCA GGCTGCAGAA  
451 CAGCGTTTCG ATGCGGCACG CGAAGAATTG CTGTTGAAAG TTGCCGAAAG  
501 TTATTTCAAC GTTTTACTCA GCCGAGACAC CGTTGCCGCC CATGCGGCGG

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551 AAAAAGAGGC TATGCCCAG CAGGTAAGGC AGGCGCAGGC TTTATTCAAT

601 AAAGGTGCTG CCACCGCGCT GGATATTCAC GAAGCCAAAG CCGGTTACGA

651 CAATGCCCTG GCCCAAGAAA TCGCCGTATT GGCTGAGAAA CAAACCTATG

701 AAAACCAGTT GAACGACTAC ACCGACCTGG ATAGCAAACA AATCGAGGCC

751 ATAGATACCG CCAACCTGTT GGCACGCTAT CTGCCCAAGC TGGAACGTTA

801 CAGTCTGGAT GAATGGCAGC GCATTGCCTT ATCCAACAAT CATGAATACC

851 GGATGCAGCA GCTTGCCCTG CAAAGCAGCG GACAGGCGCT TCGGGCAGCA

901 CAGAACAGCC GCTATCCAC CGTTTCTGCC CATGTCGGCT ATCAGAATAA

951 CCTCTACACT TCATCTGCGC AGAATAATGA CTACCACTAT CGGGGCAAAG

1001 GGATGAGCGT CGGCGTACAG TTGAATTTGC CGCTTTATAC CGGCGGAGAA

1051 TTGTCGGGCA AAATCCATGA AGCCGAAGCG CAATACGGGG CCGCCGAAGC

1101 ACAGCTGACC GCAACCGAGC GGCACATCAA ACTCGCCGTA CGCCAAGCTT

FIGURE 39A (suite 1)

WO 01/04150

PCT/EP00/06943

1151 ATACCGAAAG CGGTGCGGCG CGTTACCAA TCATGGCGCA AGAACGGGTT

1201 TTGGAAAGCA GCCGTTTGAA ACTGAAATCG ACCGAAACCG GCCAACAAATA

1251 CGGCATCCGC AACCGGCTGG AAGTAATACG GGCGCGGCAG GAAGTCGCCC

1301 AAGCAGAACA GAAACTGGCT CAAGCACGGT ATAAATTCAT GCTGGCTTAT

1351 TTGCGCTTGG TGAAAGAGAG CGGGTTAGGG TTGGAAACGG TATTTGCGGA

1401 ATAA

FIGURE 39A (suite 2)

FIGURE 39B  
-----

1 MTLNLMIMQ DYGISVCLTL TPYLQHELFS AMKSYFSKYI LPVSLFTLPL

51 SLSPSVSAFT LPEAWRAAQQ HSADFQASHY QRDAVRARQQ QAKAAFLPHV

101 SANASYQRQP PSISSTRETQ GWSVQVGQTL FDAAKFAQYR QSRFDTQAAE

151 QRFDAAREEL LLKVAESYFN VLLSRDTVAA HAAKEEAYA QVRQAQALFN

201 KGAATALDIH EAKAGYDNAL AQEIAVLAEK QTYENQLNDY TOLDSKQIEA

251 IDTANLLARY LPKLERYSLD EWQRIALSNN HEYRMOQLAL QSSGQALRAA

301 QNSRYPTVSA HVGYNLNYT SSAQNNDYHY RGKGMSVGVQ LNLPLYTGGE

351 LSGKIHEAEA QYGAAEQLT ATERHIKLAV RQAYTESGAA RYQIMAQERV

401 LESSRLKLS TETGQQYGR NRLEVIRARQ EVAQAEQKLA QARYKFMLAY

451 LRLVKESGLG LETVFAE\*

FIGURE 40 A

1 ATGACATTGC TCAATCTAAT GATAATGCAA GATTACGGTA TTTCCGTTTG  
51 CCTGACACTG ACGCCCTATT TGCAACATGA ACTATTTTCG GCTATGAAAT  
101 CCTATTTTTC CAAATATATC CTACCCGTTT CACTTTTAC CTTGCCACTA  
151 TCCCTTTCCC CATCCGTTTC GGCTTTTACG CTGCCTGAAG CATGGCGGGC  
201 GGCGCAGCAA CATTGCGCTG ATTTTCAAGC GTCCATTAC CAGCGTGATG  
251 CAGTGCGCGC ACGGCAACAA CAAGCCAAGG CCGCATTCTT TCCCCATGTA  
301 TCCGCCAATG CCAGCTACCA GCGCCAGCCG CCATCGATTT CTTCCACCCG  
351 CGAAACACAG GGATGGAGCG TGCAGGTGGG ACAAACCTTA TTTGACGCTG  
401 CCAAATTTGC ACAATACCGC CAAAGCAGGT TCGATACGCA GGCTGCAGAA  
451 CAGCGTTTCG ATGCGGCACG CGAAGAATTG CTGTTGAAAG TTGCCGAAAG  
501 TTATTTCAAC GTTTTACTCA GCCGAGACAC CGTTGCCGCC CATGCGGCGG

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551 AAAAAGAGGC TTATGCCAG CAGGTAAGGC AGGCGCAGGC TTTATTCAAT

601 AAAGGTGCTG CCACCGCGCT GGATATTCAC GAAGCCAAAG CCGGTTACGA

651 CAATGCCCTG GCCCAAGAAA TCGCCGTATT GGCTGAGAAA CAAACCTATG

701 AAAACCAGTT GAACGACTAC ACCGACCTGG ATAGCAAACA AATCGAGGCC

751 ATAGATACCG CCAACCTGTT GGCACGCTAT CTGCCCAAGC TGGAACGTTA

801 CAGTCTGGAT GAATGGCAGC GCATTGCCTT ATCCAACAAT CATGAATACC

851 GGATGCAGCA GCTTGCCCTG CAAAGCAGCG GACAGGCGCT TCGGGCAGCA

901 CAGAACAGCC GCTATCCAC CGTTTCTGCC CATGTGCGCT ATCAGAATAA

951 CCTCTACACT TCATCTGCGC AGAATAATGA CTACCACTAT CGGGGCAAAG

1001 GGATGAGCGT CGGCGTACAG TTGAATTTGC CGCTTTATAC CGGCGGAGAA

1051 TTGTGCGGCA AAATCCATGA AGCCGAAGCG CAATACGGGG CCGCCGAAGC

1101 ACAGCTGACC GCAACCGAGC GGCACATCAA ACTCGCCGTA CGCCAGGCTT

FIGURE 40A (suite 1)

1151 ATACCGAAAG CGGTGCGGCG CGTTACCAA TCATGGCGCA AGAACGGGTT  
1201 TTGGAAAGCA GCCGTTTGAA ACTGAAATCG ACCGAAACCG GCCAACAATA  
1251 CGGCATCCGC AACCGGCTGG AAGTAATACG GCGCGGCAG GAAGTCGCCC  
1301 AAGCAGAACA GAAACTGGCT CAAGCACGGT ATAAATTCAT GCTGGCTTAT  
1351 TTGCGCTTGG TGAAAGAGAG CGGGTTAGGG TTGGAAACGG TATTTGCGGA  
1401 ATAA

FIGURE 40A (suite 2)

## FIGURE 40B

1 MTLNLNLMIMQ DYGISVCLTL TPYLQHELFS AMKSYFSKYI LPVSLFTLPL

51 SLSPSVSAFT LPEAWRAAQ HSAFQASHY QRDAVRARQQ QAKAAFLPHV

101 SANASYQRQP PSISSTRETQ GWSVQVGQTL FDAAKFAQYR QSRFDTQAAE

151 QRFDAAREEL LLKVAESYFN VLLSRDTVAA HAAKEEAYA QVRQAQALFN

201 KGAATALDIH EAKAGYDNAL AQEIAVLAEK QTYENQLNDY TDLSKQIEA

251 IDTANLLARY LPKLERYS LD EWQRIALSNN HEYRMQQLAL QSSGQALRAA

301 QNSRYPTVSA HVGYNLYT SSAQNNDYHY RGKGMSVGVQ LNLPLYTGGE

351 LSGKIHAEAE QYGAAEAQLT ATERHIKLA V RQAYTESGAA RYQIMAQERV

401 LESSRLKLKS TETGQQYGIR NRLEVIRARQ EVAQAEQKLA QARYKFMLAY

451 LRLVKESGLG LETVFAE\*



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FIGURE 41A

1 ATGACATTGC TCAATCTAAT GATAATGCAA GATTACGGTA TTTCCGTTTG  
 51 CCTGACACTG ACGCCCTATT TGCAACATGA ACTATTTTCG GCTATGAAAT  
 101 CCTATTTTTC CAAATATATC CTACCCGTTT CACTTTTTAC CTTGCCACTA  
 151 TCCCTTTCCC CATCCGTTTC GGCTTTTACG CTGCCTGAAG CATGGCGGGC  
 201 GGCGCAGCAA CATTGCGCTG ATTTTCAAGC GTCCCATTAC CAGCGTGATG  
 251 CAGTGCGCGC ACGGCAACAA CAAGCCAAGG CCGCATTCCT TCCCCATGTA  
 301 TCCGCCAATG CCAGCTACCA GCGCCAGCCG CCATCGATTT CTTCCACCCG  
 351 CGAAACACAG GGATGGAGCG TGCAGGTGGG ACAAACCTTA TTTGACGCTG  
 401 CCAAATTTGC ACAATACCGC CAAAGCAGGT TCGATACGCA GGCTGCAGAA  
 451 CAGCGTTTCG ATGCGGCACG CGAAGAATTG CTGTTGAAAG TTGCCGAAAG  
 501 TTATTTCAAC GTTTTACTCA GCCGAGACAC CGTTGCCGCC CATGCGGCGG

551 AAAAAGAGGC TTATGCCAG CAGGTAAGGC AGGCGCAGGC TTTATTCAAT

601 AAAGGTGCTG CCACCGCGCT GGATATTCAC GAAGCCAAAG CCGGTTACGA

651 CAATGCCCTG GCCCAAGAAA TCGCCGTATT GGCTGAGAAA CAAACCTATG

701 AAAACCAAGTT GAACGACTAC ACCGACCTGG ATAGCAAACA AATCGAGGCC

751 ATAGATACCG CCAACCTGTT GGCACGCTAT CTGCCAAGC TGGAACGTTA

801 CAGTCTGGAT GAATGGCAGC GCATTGCCTT ATCCAACAAT CATGAATACC

851 GGATGCAGCA GCTTGCCCTG CAAAGCAGCG GACAGGCGCT TCGGGCAGCA

901 CAGAACAGCC GCTATCCAC CGTTTCTGCC CATGTCGGCT ATCAGAATAA

951 CCTCTACACT TCATCTGCGC AGAATAATGA CTACCACTAT CGGGGCAAAG

1001 GGATGAGCGT CGGCGTACAG TTGAATTTGC CGCTTTATAC CGGCGGAGAA

1051 TTGTCGGGCA AAATCCATGA AGCCGAAGCG CAATACGGGG CCGCCAAGC

1101 ACAGCTGACC GCAACCGAGC GGCACATCAA ACTCGCCGTA CGCCAGGCTT

1151 ATACCGAAAG CGGTGCGGCG CGTTACCAAA TCATGGCGCA AGAACGGGTT

1201 TTGGAAAGCA GCCGTTTGAA ACTGAAATCG ACCGAAACCG GCCAACAATA

1251 CGGCATCCGC AACCGGCTGG AAGTAATACG GCGCGGCAG GAAGTCGCC

1301 AAGCAGAACA GAACTGGCT CAAGCACGGT ATAAATTCAT GCTGGCTTAT

1351 TTGCGCTTGG TGAAAGAGAG CGGGTTAGGG TTGGAAACGG TATTTGCGGA

1401 ATAA

FIGURE 41A (suite 2)

FIGURE 41B  
-----

1 MTLNLNLMIMQ DYGISVCLTL TPYLQHELFS AMKSYFSKYI LPVSLFTLPL

51 SLSPSVSAFT LPEAWRAAQQ HSADFQASHY QRDAVRARQQ QAKAAFLPHV

101 SANASYQRQP PSISSTRETQ GWSVQVGQTL FDAAKFAQYR QSRFDTQAAE

151 QRFDAAREEL LLKVAESYFN VLLSRDTVAA HAAEKEAYA QVRQAQALFN

201 KGAATALDIH EAKAGYDNAL AQEIAVLAEK QTYENQLNDY TOLDSKQIEA

251 IDTANLLARY LPKLERYSLD EWQRIALSNN HEYRMQQLAL QSSGQALRAA

301 QNSRYPTVSA HVGYQNNLYT SSAQNNDYHY RGKGMVSGVQ LNLPLYTGGE

351 LSGKIHEAEA QYGAAEAQLT ATERHIKLAV RQAYTESGAA RYQIMAQERV

401 LESSRLKLKS TETGQQYGIR NRLEVIRARQ EVAQAEQKLA QARYKFMLAY

451 LRLVKESGLG LETVFAE\*

## FIGURE 42A

1 ATGACATTGC TCAATCTAAT GATAATGCAA GATTACGGTA TTTCCGTTTG  
51 CCTGACACTG ACGCCCTATT TGCAACATGA ACTATTTTCG GCTATGAAAT  
101 CCTATTTTTC CAAATATATC CTACCCGTTT CACTTTTTAC CTTGCCACTA  
151 TCCCTTTCCC CATCCGTTTC GGCTTTTACG CTGCCTGAAG CATGGCGGGC  
201 GGCGCAGCAA CATTGCGTG ATTTTCAAGC GTCCCATTAC CAGCGTGATG  
251 CAGTGCGCGC ACGGCAACAA CAAGCCAAGG CCGCATTCCT TCCCCATGTA  
301 TCCGCCAATG CCAGCTACCA GCGCCAGCCG CCATCGATTT CTTCCACCCG  
351 CGAAACACAG GGATGGAGCG TGCAGGTGGG ACAAACCTTA TTTGACGCTG  
401 CCAAATTTGC ACAATACCGC CAAAGCAGGT TCGATACGCA GGCTGCAGAA  
451 CAGCGTTTCG ATGCGGCACG CGAAGAATTG CTGTTGAAAG TTGCCGAAAG  
501 TTATTTCAAC GTTTTACTCA GCCGAGACAC CGTTGCCGCC CATGCGGCGG

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551 AAAAAGAGGC TTATGCCCAG CAGGTAAGGC AGGCGCAGGC TTTATTCAAT

601 AAAGGTGCTG CCACGCGCT GGATATTCAC GAAGCCAAAG CCGGTTACGA

651 CAATGCCCTG GCCAAGAAA TCGCCGTATT GGCTGAGAAA CAAACCTATG

701 AAAACCAGTT GAACGACTAC ACCGACCTGG ATAGCAAACA AATCGAGGCC

751 ATAGATACCG CCAACCTGTT GGCACGCTAT CTGCCCAAGC TGGAACGTTA

801 CAGTCTGGAT GAATGGCAGC GCATTGCCTT ATCCAACAAT CATGAATACC

851 GGATGCAGCA GCTTGCCCTG CAAAGCAGCG GACAGGCGCT TCGGGCAGCA

901 CAGAACAGCC GCTATCCAC CGTTTCTGCC CATGTCGGCT ATCAGAATAA

951 CCTCTACACT TCATCTGCGC AGAATAATGA CTACCACTAT CGGGGCAAAG

1001 GGATGAGCGT CGGCGTACAG TTGAATTTGC CGCTTTATAC CGGCGGAGAA

1051 TTGTCGGGCA AAATCCATGA AGCCGAAGCG CAATACGGGG CCGCCGAAGC

1101 ACAGCTGACC GCAACCGAGC GGCACATCAA ACTCGCCGTA CGCCAGGCTT

FIGURE 42A (suite 1)

1151 ATACCGAAAG CGGTGCGGCG CGTTACCAA TCATGGCGCA AGAACGGGTT  
1201 TTGGAAAGCA GCCGTTTGAA ACTGAAATCG ACCGAAACCG GCCAACATA  
1251 CGGCATCCGC AACCGGCTGG AAGTAATACG GCGCGGCAG GAAGTCGCC  
1301 AAGCAGAACA GAAACTGGCT CAAGCACGGT ATAAATTCAT GCTGGCTTAT  
1351 TTGCGCTTGG TGAAAGAGAG CGGGTTAGGG TTGGAAACGG TATTTGCGGA  
1401 ATAA

FIGURE 42A (suite 2)

## FIGURE 42B

1 MTLLNLMIMQ DYGISVCLTL TPYLQHELFS AMKSYFSKYI LPVSLFTLPL  
51 SLSPSVSAFT LPEAWRAAQQ HSADFQASHY QRDAVRARQQ QAKAAFLPHV  
101 SANASYQRQP PSISSTRETQ GWSVQVGQTL FDAAKFAQYR QSRFDTQAAE  
151 QRFDAAREEL LLKVAESYFN VLLSRDTVAA HAAEKEAYAQ QVRQAQALFN  
201 KGAATALDIH EAKAGYDNAL AQEIAVLAEK QTYENQLNDY TOLDSKQIEA  
251 IDTANLLARY LPKLERYSLD EWQRIALSNN HEYRMQQLAL QSSGQALRAA  
301 QNSRYPTVSA HVGYNLNYT SSAQNNDYHY RGKGMVGVQ LNLPLYTGGE  
351 LSGKIHEAEA QYGAAEAQLT ATERHIKLA V RQAYTESGAA RYQIMAQERV  
401 LESSRLKLKS TETGQQYGIR NRLEVIRARQ EVAQAEQKLA QARYKFMLAY  
451 LRLVKESGLG LETVFAE\*



FIGURE 43 A  
-----

1 ATGACATTGC TCAATCTAAT GATAATGCAA GATTACGGTA TTTCCGTTTG  
51 CCTGACACTG ACGCCCTATT TGCAACATGA ACTATTTTCG GCTATGAAAT  
101 CCTATTTTTC CAAATATATC CTACCCGTTT CACTTTTAC CTTGCCACTA  
151 TCCCTTTCCC CATCCGTTTC GGCTTTTACG CTGCCTGAAG CATGGCGGGC  
201 GGCGCAGCAA CATTGGGCTG ATTTTCAAGC GTCCCATTA CAGCGTGATG  
251 CAGTGCGCGC ACGGCAACAA CAAGCCAAGG CCGCATTCCT TCCCCATGTA  
301 TCCGCCAATG CCAGCTACCA GCGCCAGCCG CCATCGATTT CTTCCACCCG  
351 CGAAACACAG GGATGGAGCG TGCAGGTGGG ACAAACCTTA TTTGACGCTG  
401 CCAAATTTGC ACAATACCGC CAAAGCAGGT TCGATACGCA GGCTGCAGAA  
451 CAGCGTTTCG ATGCGGCACG CGAAGAATTG CTGTTGAAAG TTGCCGAAAG  
501 TTATTTCAAC GTTTTACTCA GCCGAGACAC CGTTGCCGCC CATGCGGCGG

551 AAAAAGAGGC TTATGCCAG CAGGTAAGGC AGGCGCAGGC TTTATTCAAT

601 AAAGGTGCTG CCACCGCGCT GGATATTCAC GAAGCCAAAG CCGGTTACGA

651 CAATGCCCTG GCCCAAGAAA TCGCCGTATT GGCTGAGAAA CAAACCTATG

701 AAAACCAAGTT GAACGACTAC ACCGACCTGG ATAGCAAACA AATCGAGGCC

751 ATAGATACCG CCAACCTGTT GGCACGCTAT CTGCCAAGC TGGAACGTTA

801 CAGTCTGGAT GAATGGCAGC GCATTGCCTT ATCCAACAAT CATGAATACC

851 GGATGCAGCA GCTTGCCCTG CAAAGCAGCG GACAGGCGCT TCGGGCAGCA

901 CAGAACAGCC GCTATCCAC CGTTTCTGCC CATGTGGCT ATCAGAATAA

951 CCTCTAACT TCATCTGCGC AGAATAATGA CTACCACTAT CGGGGCAAAG

1001 GGATGAGCGT CGGCGTACAG TTGAATTGCG CGCTTTATAC CGGCGGAGAA

1051 TTGTCGGGCA AAATCCATGA AGCCGAAGCG CAATACGGGG CCGCCGAAGC

1101 ACAGCTGACC GCAACCGAGC GGCACATCAA ACTCGCCGTA CGCCAGGCTT

FIGURE 43A (suite 1)

1151 ATACCGAAAG CGGTGCGGCG CGTTACCAA TCATGGCGCA AGAACGGGTT

1201 TTGGAAAGCA GCCGTTTGAA ACTGAAATCG ACCGAAACCG GCCAACAATA

1251 CGGCATCCGC AACCGGCTGG AAGTAATACG GCGCGGCAG GAAGTCGCCC

1301 AAGCAGAACA GAAACTGGCT CAAGCACGGT ATAAATTCAT GCTGGCTTAT

1351 TTGCGCTTGG TGAAAGAGAG CGGGTTAGGG TTGAAACGG TATTTGCGGA

1401 ATAA

FIGURE 43A (suite 2)

## FIGURE 43B

1 MTLNLNMIQ DYGISVCLTL TPYLQHELFS AMKSYFSKYI LPVSLFTLPL

51 SLSPSVSAFT LPEAWRAAQ HSADFQASHY QRDAVRARQQ QAKAAFLPHV

101 SANASYQRQP PSISSTRETQ GWSVQVGQTL FDAAKFAQYR QSRFDTQAAE

151 QRFDAAREEL LLKVAESYFN VLLSRDTVAA HAAEKEAYAQ QVRQAQALFN

201 KGAATALDIH EAKAGYDNAL AQEIAVLAEK QTYENQLNDY TDLDISKQIEA

251 IDTANLLARY LPKLERYSLD EWQRIALSNN HEYRMQQLAL QSSGQALRAA

301 QNSRYPTVSA HVGYNQNNLYT SSAQNNDYHY RGKGMSVGVQ LNLPLYTGGE

351 LSGKIHEAEA QYGAAEAQLT ATERHIKLAV RQAYTESGAA RYQIMAQERV

401 LESSRLKLKS TETGQQYGIR NRLEVIRARQ EVAQAEQKLA QARYKFMLAY

451 LRLVKESGLG LETVFAE\*

FIGURE 44A

1 ATGACATTGC TCAATCTAAT GATAATGCAA GATTACGGTA TTTCCGTTTG  
51 CCGGACACTG ACGCCCTATT TGCAACATGA ACTATTTTCG GCTATGAAAT  
101 CCTATTTTTC CAAATATATC CTACCCGTTT CACTTTTAC CTTGCCACTA  
151 TCCCTTTCCC CATCCGTTTC GGCTTTTACG CTGCTGAAG CATGGCGGGC  
201 GCGCAGCAA CATTCGGCTG ATTTTCAAGC GTCCATTAC CAGCGTGATG  
251 CAGTGCGCGC ACGGCAACAA CAAGCCAAGG CCGCATTCTT TCCCATGTA  
301 TCCGCCAATG CCAGCTACCA GCGCCAGCCG CCATCGATTT CTTCACCCG  
351 CGAAACACAG GGATGGAGCG TGCAGGTGGG ACAAACCTTA TTTGACGCTG  
401 CCAAATTTGC ACAATACCGC CAAAGCAGGT TCGATACGCA GGCTGCAGAA  
451 CAGCGTTTCG ATGCGGCACG CGAAGAATTG CTGTTGAAAG TTGCCGAAAG  
501 TTATTTCAAC GTTTTACTCA GCCGAGACAC CGTTGCCGCC CATGCGGCGG

551 AAAAAGAGGC TTATGCCAG CAGTAAGGC AGGCGCAGGC TTTATTCAAT

601 AAAGGTGCTG CCACCGCGCT GGATATTCAC GAAGCCAAAG CCGTTACGA

651 CAATGCCCTG GCCCAAGAAA TCGCCGTATT GGCTGAGAAA CAAACCTATG

701 AAAACCAAGT GAACGACTAC ACCGACCTGG ATAGCAAACA AATCGAGGCC

751 ATAGATACCG CCAACCTGTT GGCACGCTAT CTGCCAAGC TGGAACGTTA

801 CAGTCTGGAT GAATGGCAGC GCATTGCCTT ATCCAACAAT CATGAATACC

851 GGATGCAGCA GCTTGCCCTG CAAAGCAGCG GACAGGCGCT TCGGGCAGCA

901 CAGAACAGCC GCTATCCAC CGTTTCTGCC CATGTCGGCT ATCAGAATAA

951 CCTCTACACT TCATCTGCGC AGAATAATGA CTACCACTAT CGGGGCAAAG

1001 GGATGAGCGT CGGCGTACAG TTGAATTTGC CGCTTTATAC CGGCGGAGAA

1051 TTGTCGGGCA AAATCCATGA AGCCGAAGCG CAATACGGGG CCGCCAAGC

1101 ACAGCTGACC GCAACCGAGC GGCACATCAA ACTCGCCGTA CGCCAGGCTT

FIGURE 44B  
-----

1 MTLNLNMIMQ DYGISVCLTL TPYLQHELFS AMKSYFSKYI LPVSLFTLPL

51 SLSPSVSAFT LPEAWRAAQQ HSADFQASHY QRDAVRARQQ QAKAAFLPHV

101 SANASYQRQP PSISSTRETQ GWSVQVGQTL FDAAKFAQYR QSRFDTQAAE

151 QRFDAAREEL LLKVAESYFN VLLSRDTVAA HAAEKEAYA QVRQAQALFN

201 KGAATALDIH EAKAGYDNAL AQEIAVLAEK QTYENQLNDY TDLSKQIEA

251 IDTANLLARY LPKLERYSLD EWQRIALSNN HEYRMQQLAL QSSGQALRAA

301 QNSRYPTVSA HVGYNQNNLYT SSAQNNDYHY RGKGMSVGVQ LNLPLYTGGE

351 LSGKIHAEAE QYGAAEQLT ATERHIKLAV RQAYTESGAA RYQIMAQERV

401 LESSRLKLKS TETGQQYGIR NRLEVIRARQ EVAQAEQKLA QARYKFMLAY

451 LRLVKESGLG LETVFAE\*

1151 ATACCGAAAG CGGTGCGGCG CGTTACCAAA TCATGGCGCA AGAACGGGTT  
1201 TTGGAAAGCA GCCGTTTGAA ACTGAAATCG ACCGAAACCG GCCAACAATA  
1251 CGGCATCCGC AACCGGCTGG AAGTAATACG GGCGCGGCAG GAAGTCGCCC  
1301 AAGCAGAACA GAAACTGGCT CAAGCACGGT ATAAATTCAT GCTGGCTTAT  
1351 TTGCGCTTGG TGAAAGAGAG CGGGTTAGGG TTGGAAACGG TATTTGCGGA  
1401 ATAA

FIGURE 44B (suite)



## FIGURE 45A

1 ATGACATTGC TCAATCTAAT GATAATGCAA GATTACGGTA TTTCCGTTTG  
51 CCTGACACTG ACGCCCTATT TGCAACATGA ACTATTTTCG GCTATGAAAT  
101 CCTATTTTTC CAAATATATC CTACCCGTTT CACTTTTTAC CTTGCCACTA  
151 TCCCTTTCCC CATCCGTTTC GGCTTTTACG CTGCCTGAAG CATGGCGGGC  
201 GCGCAGCAA CATTGCGCTG ATTTTCAAGC GTCCATTAC CAGCGTGATG  
251 CAGTGCGCGC ACGGCAACAA CAAGCCAAGG CCGCATTCTT TCCCCATGTA  
301 TCCGCCAATG CCAGCTACCA GCGCCAGCCG CCATCGATTT CTTCCACCCG  
351 CGAAACACAG GGATGGAGCG TGCAGGTGGG ACAAACCTTA TTTGACGCTG  
401 CCAAATTTGC ACAATACCGC CAAAGCAGGT TCGATACGCA GGCTGCAGAA  
451 CAGCGTTTCG ATGCGGCACG CGAAGAATTG CTGTTGAAAG TTGCCGAAAG  
501 TTATTTCAAC GTTTTACTCA GCCGAGACAC CGTTGCCGCC CATGCGGCGG

551 AAAAAGAGGC TTATGCCAG CAGGTAAGGC AGGCGCAGGC TTTATTCAAT

601 AAAGGTGCTG CCACCGCGCT GGATATTCAC GAAGCCAAAG CCGGTTACGA

651 CAATGCCCTG GCCCAAGAAA TCGCCGTATT GGCTGAGAAA CAAACCTATG

701 AAAACCAGTT GAACGACTAC ACCGACCTGG ATAGCAAACA AATCGAGGCC

751 ATAGATACCG CCAACCTGTT GGCACGCTAT CTGCCCAAGC TGGAACGTTA

801 CAGTCTGGAT GAATGGCAGC GCATTGCCTT ATCCAACAAT CATGAATACC

851 GGATGCAGCA GCTTGCCCTG CAAAGCAGCG GACAGGCGCT TCGGGCAGCA

901 CAGAACAGCC GCTATCCAC CGTTTCTGCC CATGTGCGCT ATCAGAATAA

951 CCTCTACACT TCATCTGCGC AGAATAATGA CTACCACTAT CGGGGCAAAG

1001 GGATGAGCGT CGGCGTACAG TTGAATTTGC CGCTTTATAC CGGCGGAGAA

1051 TTGTCGGGCA AAATCCATGA AGCCGAAGCG CAATACGGGG CCGCCGAAGC

1101 ACAGCTGACC GCAACCGAGC GGCACATCAA ACTCGCCGTA CGCCAGGCTT

1151 ATACCGAAAG CGGTGCGGCG CGTTACCAA TCATGGCGCA AGAACGGGTT

1201 TTGGAAAGCA GCCGTTTGAA ACTGAAATCG ACCGAAACCG GCCAACAATA

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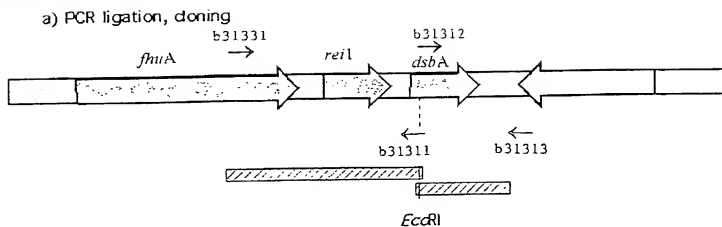
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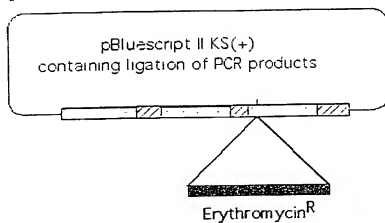
FIGURE 45A (suite 2)

## FIGURE 45 B

1 MTLNLNMIMQ DYGISVCLTL TPYLQHELFS AMKSYFSKYI LPVSLFTLPL  
51 SLSPSVSAFT LPEAWRAAQ HSAOFQASHY QRDAVRARQQ QAKAAFLPHV  
101 SANASYQRQP PSISSTRETQ GWSVQVGQTL FDAAKFAQYR QSRFDTQAAE  
151 QRFDAAREEL LLKVAESYFN VLLSRDTVAA HAAEKEAYA QVRQAQALFN  
201 KGAATALDIH EAKAGYDNAL AQEIAVLAEK QTYENQLNDY TOLDSKQIEA  
251 IDTANLLARY LPKLERYSLD EWQRIALSNN HEYRMQQLAL QSSGQALRAA  
301 QNSRYPTVSA HVGYQNNLYT SSAQNNDYHY RGKGMVSGVQ LNLPLYTGGE  
351 LSGKIHAEAE QYGAAEAQLT ATERHIKLAV RQAYTESGAA RYQIMAQERV  
401 LESSRLKLKS TETGQQYGIR NRLEVIRARQ EVAQAEQKLA QARYKFMLAY  
451 LRLVKESGLG LETVFAE\*



b) Insertion of erythromycin resistance cassette



c) Transformation of *Nm* to erythromycin resistance and DsbA1<sup>-</sup>

Figure 46

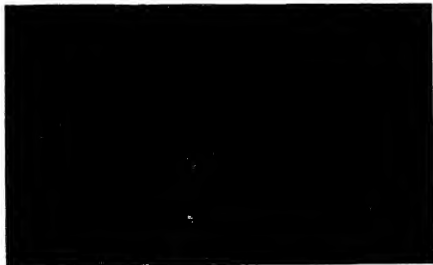


Figure 47A

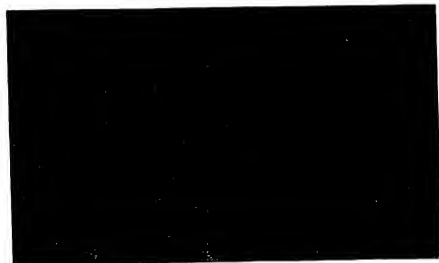


Figure 47B

10/030740

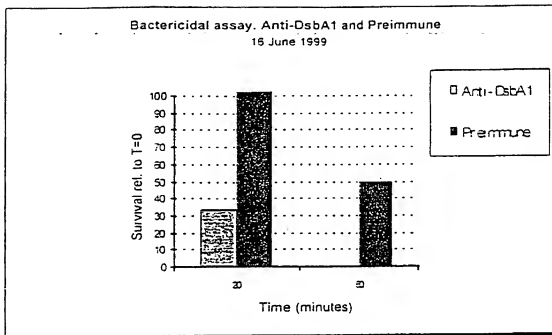


Figure 48

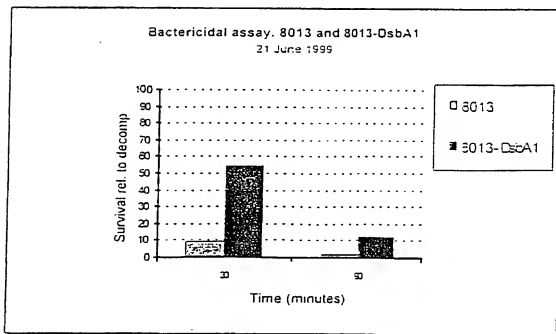


Figure 49

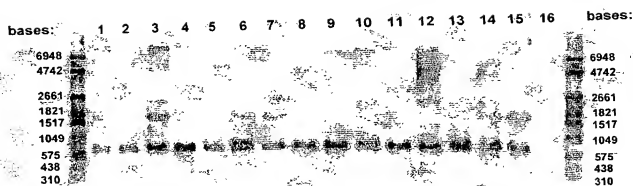


Figure 50



Rec'd PCT/PTO 27 MAR 2002

Nixon &amp; Vandenberg P.C. (10/99)

Domestic Non-Assignee/Foreigner Page 1

RULE 63 (37 C.F.R. 1.53)  
INVENTORS DECLARATION FOR PATENT APPLICATION  
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

I, a below named inventor, hereby declare that my residence, mailing address and citizenship are as stated below next to my name, and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **Noval Nesseria Meningitidis compounds and anti-infection applications thereof.**

Specification of which (check applicable box(es))

is attached hereto  
was filed on \_\_\_\_\_ as U.S. Application Serial No. \_\_\_\_\_ (Am. Orl. No. 721-09)  
was filed as PCT International application No. **PCT/EP00/06943** on **July 5, 2000**  
is (if applicable to U.S. or PCT application) was amended on **23 August 2001**

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose to the Patent Office all information known to me to be material to patentability as defined in 37 C.F.R. 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119/165 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed or, if no priority is claimed, before the filing date of this application.

Application Number	Country	Date/Month/Year Filed
99 401 766.8	Europe	13 July 1999

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below

Application Number	Date/Month/Year Filed	Status: patented pending, abandoned Pending
<b>PCT/EP00/06943</b>	<b>5 July 2000</b>	<b>Patented</b>

I hereby claim the benefit under 35 U.S.C. 120/365 of all prior United States and PCT international applications listed above or below

For U.S./PCT Application(s).

Application Serial No.	Date/Month/Year Filed	Status: patented pending, abandoned Pending
<b>PCT/EP00/06943</b>	<b>5 July 2000</b>	<b>Patented</b>

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that all statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issued thereon. And on behalf of the owner(s) hereof, I hereby appoint NIXON & VANDENBERG P.C., 1100 North Glebe Rd., Falls Church, VA 22046, a telephone number (703) 816-4000 (to whom all communications are to be directed), and the following (attorneys-in-fact (of the same address)) individually and collectively owner's attorneys to prosecute this application and to transact all business the Patent and Trademark Office connected therewith and with the resulting patent. Larry S. Nixon, 25640, Arthur R. Crawford, 25327, James T. Gosmer, 31184, Robert W. Fens, 31184, Richard G. Besha, 24720, Mark E. Husbbaum, 32248, Michael J. Kaenan, 32106, Bryan H. Davidson, 32623, Anthony C. Spooner, 37393, Leonard C. Michard, 29009, Duane M. Byers, 33387, Jeffrey H. Nelson, 30441, John R. Laksova, 32149, M. Warren Buman, 29366, Mary J. Wilson, 32955, J. Scott Davidson, 31149, John M. Hagen, 36128, Robert A. Moran, 29834, B. J. Sadoff, 36665, James O. Beroult, 2778, Upstead S. Gill, 37334, Michael J. Shea, 34725, Donald L. Jackson, 45090, Michelle N. Lester, 32231, Frank P. Prestia, 12828, Joseph S. Prestia, 33320, Joseph A. Rhoads, 37515, Raymond Y. Ma, 41426, Chris Compton, 31387, Gary T. Taniguchi, 43780. I also authorize Nixon & Vandenberg to state any attorney names/numbers no longer with the firm and to act and rely solely on instructions directly communicated from the inventor, assignee, owner, firm, or other organization sending instructions to Nixon & Vandenberg on behalf of the owner(s).

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Inventor: THANLEX (first) French (citizenship)

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(Zip Code) F-75015

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Inventor: KLEE (first) German (citizenship)

Residence (city): Berlin (state/country): Germany DEX  
Mailing Address: Isenburger Weg 65C  
(Zip Code) D-13591

☒ See attached sheet(s) for additional inventor(s) information!!

Nixon & Vanderhys P.C. (10/99)  
 (Domestic Non-Assigned/Foreign)  
 Page 2

Serial No.

4-00

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 Inventor

Mark A. Achten

Date

March 13, 2002

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Date

20/03/02

Petra

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Germany

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(Zip Code)

D-10435

## SEQUENCE LISTING

&lt;110&gt; I. N. S. E. R. M.

MAX-PLANCK-GESELLSCHAFT ZUR FÖRDERUNG DES WISSENS

<120> Novel *Neisseria meningitidis* compounds and  
anti-infection applications thereof

&lt;130&gt; 989 SEQUENCES

&lt;140&gt;

&lt;141&gt;

&lt;160&gt; 116

&lt;170&gt; PatentIn Ver. 2.1

&lt;210&gt; 1

&lt;211&gt; 696

&lt;212&gt; DNA

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&lt;400&gt; 1

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Ala Ala Cys Ser Lys Gln Ala Glu Thr Ser Val Pro Ala Asp Ser Ala
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&lt;211&gt; 231

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<213> *Neisseria meningitidis*

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```

```

Gln Ser Ser Ser Ala Pro Ala Ala Pro Ala Glu Leu Asn Glu Gly
  35              40              45

```

```

Val Asn Tyr Thr Val Leu Ser Thr Pro Ile Pro Gln Gln Ala Gly
  50              55              60

```

```

Lys Ile Glu Val Leu Glu Phe Phe Gly Tyr Phe Cys Pro His Cys Ala
  65              70              75              80

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His Leu Glu Pro Val Leu Ser Glu His Ile Lys Thr Phe Lys Asp Asp
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Thr Tyr Met Arg Arg Glu His Val Val Trp Gly Asp Glu Met Lys Pro
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Leu Ala Arg Leu Ala Ala Ala Val Glu Met Ala Gly Glu Ser Asp Lys
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Ala Asp Thr Asp Thr Leu Lys Lys Trp Leu Ser Glu Gln Thr Ala Phe
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Asp Gly Lys Lys Val Leu Ala Ala Phe Glu Ala Pro Glu Ser Gln Ala

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Trp Gln Ser Gly Met Thr Thr Ile Asp Gln Leu Val Asp Lys Val Arg  
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Glu Glu Gln Lys Lys Pro Gln  
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Gln Ser Ser Ser Ser Ala Pro Ala Ala Pro Ala Glu Leu Asn Glu Gly  
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Lys Ile Glu Val Leu Glu Phe Phe Gly Tyr Phe Cys Pro His Cys Ala
   65                               70                               75                               80

His Leu Glu Pro Val Leu Ser Glu His Ile Lys Thr Phe Lys Asp Asp
           85                               90                               95

Thr Tyr Met Arg Arg Glu His Val Trp Gly Asp Glu Met Lys Pro
   100                               105                               110

Leu Ala Arg Leu Ala Ala Ala Val Glu Met Ala Gly Glu Ser Asp Lys
   115                               120                               125

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   130                               135                               140

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Glu Glu Gln Lys Lys Pro Gln
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WO 01/04150

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Met Lys Leu Lys Thr Leu Ala Leu Thr Ser Leu Thr Leu Leu Ala Leu  
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Ala Ala Cys Ser Lys Gln Ala Glu Thr Ser Val Pro Ala Asp Ser Ala  
 20 25 30

Gln Ser Ser Ser Ser Ala Pro Ala Ala Pro Ala Glu Leu Asn Glu Gly  
 35 40 45

Val Asn Tyr Thr Val Leu Ser Thr Pro Ile Pro Gln Gln Gln Ala Gly  
 50 55 60

Lys Ile Glu Val Leu Glu Phe Phe Gly Tyr Phe Cys Pro His Cys Ala  
 65 70 75 80

His Leu Glu Pro Val Leu Ser Glu His Ile Lys Thr Phe Lys Asp Asp  
 85 90 95

Thr Tyr Met Arg Arg Glu His Val Val Trp Gly Asp Glu Met Lys Pro  
 100 105 110

Leu Ala Arg Leu Ala Ala Ala Val Glu Met Ala Gly Glu Ser Asp Lys  
 115 120 125

Ala Asn Ser His Ile Phe Asp Ala Met Val Asn Gln Lys Ile Asn Leu  
 130 135 140

Ala Asp Thr Asp Thr Leu Lys Lys Trp Leu Ser Glu Gln Thr Ala Phe  
 145 150 155 160

Asp Gly Lys Lys Val Leu Ala Ala Phe Glu Ala Pro Glu Ser Gln Ala  
 165 170 175



Arg Ala Ala Gln Met Glu Glu Leu Thr Asn Lys Phe Gln Ile Ser Gly  
 180 185 190

Thr Pro Thr Val Ile Val Gly Gly Lys Tyr Gln Val Glu Phe Lys Asp  
 195 200 205

Trp Gln Ser Gly Met Thr Thr Ile Asp Gln Leu Val Asp Lys Val Arg  
 210 215 220

Glu Glu Gln Lys Lys Pro Gln  
 225 230

<210> 9

<211> 696

<212> DNA

<213> Neisseria meningitidis

<400> 9

atgaaactga aaaccttagc ttgacttca ttgaccctgt tggcattggc cgcttgtagc 60  
 aaacaggctg aaaccagtggt tccggcagac agcgcccaaa gcagctcacc tgctccggca 120  
 gccctgctg agttgaacga aggtgtgaac tacactgtat tgtctacgcc tattccgcaa 180  
 cagcaggccg gtaaaatcga agtattggaa ttttcggct actctgcc gcattgcgcc 240  
 catcttgagc cggtcttgag cgagcacatc aaaacgttta aagacgatac ctatatgcgc 300  
 cgggagcatg tcgtgtgggg tgatgaaatg aaacctttgg cagcttggc ggccgcagtg 360  
 gaaatggccg gtgaatcaga taaagccaac agccatattt tcgatgcgat ggtaaatcaa 420  
 aaaatcaatc tggccgatac cgataccctg aaaaaatggc tgctccgagca aacagcgctt 480  
 gacggcaaaa aagtattggc tgcatttgag gtccttgaaa gccaaagcgc tgccgctcaa 540  
 atggaagagt tgaccaataa attccaaatc agcggcacac cgactgtgat tgcggcggc 600  
 aaataccaag ttgaatttaa agactggcag tccggtatga ccacgattga ccagttggg 660  
 gataaagtac gcgaagagca gaaaagccg caataa 696

<210> 10

<211> 231

<212> PRT

<213> Neisseria meningitidis

<400> 10

Met Lys Leu Lys Thr Leu Ala Leu Thr Ser Leu Thr Leu Leu Ala Leu  
 1 5 10 15

Ala Ala Cys Ser Lys Gln Ala Glu Thr Ser Val Pro Ala Asp Ser Ala  
 20 25 30

Gln Ser Ser Ser Ser Ala Pro Ala Ala Pro Ala Glu Leu Asn Glu Gly  
 35 40 45

Val Asn Tyr Thr Val Leu Ser Thr Pro Ile Pro Gln Gln Gln Ala Gly

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50	55	60
Lys Ile Glu Val Leu Glu Phe Phe Gly Tyr Phe Cys Pro His Cys Ala		
65	70	75 80
His Leu Glu Pro Val Leu Ser Glu His Ile Lys Thr Phe Lys Asp Asp		
85	90	95
Thr Tyr Met Arg Arg Glu His Val Val Trp Gly Asp Glu Met Lys Pro		
100	105	110
Leu Ala Arg Leu Ala Ala Ala Val Glu Met Ala Gly Glu Ser Asp Lys		
115	120	125
Ala Asn Ser His Ile Phe Asp Ala Met Val Asn Gln Lys Ile Asn Leu		
130	135	140
Ala Asp Thr Asp Thr Leu Lys Lys Trp Leu Ser Glu Gln Thr Ala Phe		
145	150	155 160
Asp Gly Lys Lys Val Leu Ala Ala Phe Glu Ala Pro Glu Ser Gln Ala		
165	170	175
Arg Ala Ala Gln Met Glu Glu Leu Thr Asn Lys Phe Gln Ile Ser Gly		
180	185	190
Thr Pro Thr Val Ile Val Gly Gly Lys Tyr Gln Val Glu Phe Lys Asp		
195	200	205
Trp Gln Ser Gly Met Thr Thr Ile Asp Gln Leu Val Asp Lys Val Arg		
210	215	220
Glu Glu Gln Lys Lys Pro Gln		
225	230	

<210> 11

<211> 696

<212> DNA

<213> Neisseria meningitidis

<400> 11

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 aaacaggctg aaaccagtgt tccggcagac agcgcccaaa gcagctcatc tgctccggca 120  
 gcccttgctg agttgaacga aggtgtgaac tacactgtat tgtctacgcc tattccgcaa 180  
 cagcaggccc gtaaaatcga agtattggaa tttttcggct acttctgccc gcattgcccc 240  
 catcttgagc cggctcttgag cgagcacatc aaaacgttta aagacgatac ctatatgcgc 300  
 cgggagcatg tcgtgtgggg tgatgaaatg aaacctttgg cactgtttggc ggccgcagtg 360

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PCT/EP00/06943

gaaatggccg gtgaatcaga taaagccaac agccatattt tccgatgcgat ggtaaatcaa 420  
 aaaatcaatc tggccgatac cgataccctg aaaaaatggc tgtcccgacga aacagcggtt 480  
 gacggcaaaa aagtattggc tgcatttgag gctcctgaaa gccaaagcgcg tgcggctcaa 540  
 atggaagagt tgaccaataa attccaaatc agcggcacac cgactgtgat tgtcggcggc 600  
 aaataccaag ttgaatttaa agactggcag tccggatatga ccacgattga ccagttgggt 660  
 gataaagtac gcgaagagca gaaaaagccg caataa 696

<210> 12

<211> 231

<212> PRT

<213> *Neisseria meningitidis*

<400> 12

Met Lys Leu Lys Thr Leu Ala Leu Thr Ser Leu Thr Leu Leu Ala Leu  
 1 5 10 15

Ala Ala Cys Ser Lys Gln Ala Glu Thr Ser Val Pro Ala Asp Ser Ala  
 20 25 30

Gln Ser Ser Ser Ser Ala Pro Ala Ala Pro Ala Glu Leu Asn Glu Gly  
 35 40 45

Val Asn Tyr Thr Val Leu Ser Thr Pro Ile Pro Gln Gln Gln Ala Gly  
 50 55 60

Lys Ile Glu Val Leu Glu Phe Phe Gly Tyr Phe Cys Pro His Cys Ala  
 65 70 75 80

His Leu Glu Pro Val Leu Ser Glu His Ile Lys Thr Phe Lys Asp Asp  
 85 90 95

Thr Tyr Met Arg Arg Glu His Val Val Trp Gly Asp Glu Met Lys Pro  
 100 105 110

Leu Ala Arg Leu Ala Ala Ala Val Glu Met Ala Gly Glu Ser Asp Lys  
 115 120 125

Ala Asn Ser His Ile Phe Asp Ala Met Val Asn Gln Lys Ile Asn Leu  
 130 135 140

Ala Asp Thr Asp Thr Leu Lys Lys Trp Leu Ser Glu Gln Thr Ala Phe  
 145 150 155 160

Asp Gly Lys Lys Val Leu Ala Ala Phe Glu Ala Pro Glu Ser Gln Ala  
 165 170 175

Arg Ala Ala Gln Met Glu Glu Leu Thr Asn Lys Phe Gln Ile Ser Gly  
 180 185 190

Thr Pro Thr Val Ile Val Gly Gly Lys Tyr Gln Val Glu Phe Lys Asp  
195 200 205

Trp Gln Ser Gly Met Thr Thr Ile Asp Gln Leu Val Asp Lys Val Arg  
210 215 220

Glu Glu Gln Lys Lys Pro Gln  
225 230

<210> 13

<211> 696

<212> DNA

<213> *Neisseria meningitidis*

<400> 13

atgaaactga aaaccttagc ttgacttca ttgacctgt tggcattggc cgcttgtagc 60  
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gccctgtcgt agttgaacga agtgtgtgaac tacactgtat tgtctacgcc tattccgcaa 180  
cagcaggccg gtaaaatcga agtattggaa ttttctggct acttctgcc gcattgcgcc 240  
catcttgagc cggctcttgag cgagcacatc aaaaacgttta aagacgatac ctatatgcgc 300  
cgggagcatg tcgtgtgggg tgatgaaatg aaacctttgg cactgtttgc ggccgcagtg 360  
gaaatggccg gtgaatcaga taaagccaac agccatattt tcgatgcgat ggttaataca 420  
aaaatcaatc tggccgatac cgataccctg aaaaaatggc tgtccgagca aacagcgttt 480  
gacggcaaaa aagtattggc tgcatttgag gctcctgaaa gccaaagcgc tgcggctcaa 540  
atggaagagt tgaccaataa attccaaatc agcggcacac cgactgtgat tgcggcgccg 600  
aaataccaag ttgaatttaa agactggcag tccggtatga ccagattga ccagttgggt 660  
gataaagatc gcgaagagca gaaaaagccg caataa 696

<210> 14

<211> 231

<212> PRT

<213> *Neisseria meningitidis*

<400> 14

Met Lys Leu Lys Thr Leu Ala Leu Thr Ser Leu Thr Leu Leu Ala Leu  
1 5 10 15

Ala Ala Cys Ser Lys Gln Ala Glu Thr Ser Val Pro Ala Asp Ser Ala  
20 25 30

Gln Ser Ser Ser Ser Ala Pro Ala Ala Pro Ala Glu Leu Asn Glu Gly  
35 40 45

Val Asn Tyr Thr Val Leu Ser Thr Pro Ile Pro Gln Gln Ala Gly  
50 55 60

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Lys Ile Glu Val Leu Glu Phe Phe Gly Tyr Phe Cys Pro His Cys Ala  
65 70 75 80

His Leu Glu Pro Val Leu Ser Glu His Ile Lys Thr Phe Lys Asp Asp  
85 90 95

Thr Tyr Met Arg Arg Glu His Val Val Trp Gly Asp Glu Met Lys Pro  
100 105 110

Leu Ala Arg Leu Ala Ala Ala Val Glu Met Ala Gly Glu Ser Asp Lys  
115 120 125

Ala Asn Ser His Ile Phe Asp Ala Met Val Asn Gln Lys Ile Asn Leu  
130 135 140

Ala Asp Thr Asp Thr Leu Lys Lys Trp Leu Ser Glu Gln Thr Ala Phe  
145 150 155 160

Asp Gly Lys Lys Val Leu Ala Ala Phe Glu Ala Pro Glu Ser Gln Ala  
165 170 175

Arg Ala Ala Gln Met Glu Glu Leu Thr Asn Lys Phe Gln Ile Ser Gly  
180 185 190

Thr Pro Thr Val Ile Val Gly Gly Lys Tyr Gln Val Glu Phe Lys Asp  
195 200 205

Trp Gln Ser Gly Met Thr Thr Ile Asp Gln Leu Val Asp Lys Val Arg  
210 215 220

Glu Glu Gln Lys Lys Pro Gln  
225 230

<210> 15

<211> 696

<212> DNA

<213> Neisseria meningitidis

<400> 15

atgaaactga aaaccttagc ttgacttca ttgacctgt tggcattggc cgcttgtagc 60  
aaacaggctg aaaccagtgt tccgcgagac agcgcccaaa gcagctcacc tgctccggca 120  
gcccttgctg agttgaacga aggtgtgaac tacactgtat tgtctacgcc tattccgcaa 180  
cagcaggccg gtaaaatcga agtattggaa ttttccgct actctgccc gcattgcgcc 240  
catcttgagc cggctcttgag cgagcacatc aaaacgttta aagacgatac ctatatgcgc 300  
cgggagcatg tcgtgtgggg tgatgaaatg aaaccttttg cagctttggc ggccgcagtg 360  
gaaatggccg gtgaatcaga taaagccaac agccatattt tcgatcgat gggttaacaa 420  
aaaatcaatc tggccgatac cgataccctg aaaaaatggc tgtccgagca aacagcgttt 480

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PCT/EP00/06943

gacggcaaaa aagtattggc tgcatttgag gctcctgaaa gccaaagcgc tgcggctcaa 540  
 atggaagagt tgaccaataa attccaaatc agcggcacac cgactgtgat tgcggcggc 600  
 aaataccaag ttgaatttaa agactggcag tccggtatga ccacgattga ccagttgggtg 660  
 gataaagtac gcgaagagca gaaaaagccg caataa 696

&lt;210&gt; 16

&lt;211&gt; 231

&lt;212&gt; PRT

&lt;213&gt; Neisseria meningitidis

&lt;400&gt; 16

Met Lys Leu Lys Thr Leu Ala Leu Thr Ser Leu Thr Leu Leu Ala Leu  
 1 5 10 15

Ala Ala Cys Ser Lys Gln Ala Glu Thr Ser Val Pro Ala Asp Ser Ala  
 20 25 30

Gln Ser Ser Ser Ser Ala Pro Ala Ala Pro Ala Glu Leu Asn Glu Gly  
 35 40 45

Val Asn Tyr Thr Val Leu Ser Thr Pro Ile Pro Gln Gln Gln Ala Gly  
 50 55 60

Lys Ile Glu Val Leu Glu Phe Phe Gly Tyr Phe Cys Pro His Cys Ala  
 65 70 75 80

His Leu Glu Pro Val Leu Ser Glu His Ile Lys Thr Phe Lys Asp Asp  
 85 90 95

Thr Tyr Met Arg Glu His Val Val Trp Gly Asp Glu Met Lys Pro  
 100 105 110

Leu Ala Arg Leu Ala Ala Val Glu Met Ala Gly Glu Ser Asp Lys  
 115 120 125

Ala Asn Ser His Ile Phe Asp Ala Met Val Asn Gln Lys Ile Asn Leu  
 130 135 140

Ala Asp Thr Asp Thr Leu Lys Lys Trp Leu Ser Glu Gln Thr Ala Phe  
 145 150 155 160

Asp Gly Lys Lys Val Leu Ala Ala Phe Glu Ala Pro Glu Ser Gln Ala  
 165 170 175

Arg Ala Ala Gln Met Glu Glu Leu Thr Asn Lys Phe Gln Ile Ser Gly  
 180 185 190

Thr Pro Thr Val Ile Val Gly Gly Lys Tyr Gln Val Glu Phe Lys Asp

195

200

205

Trp Gln Ser Gly Met Thr Thr Ile Asp Gln Leu Val Asp Lys Val Arg  
 210 215 220

Glu Glu Gln Lys Lys Pro Gln  
 225 230

&lt;210&gt; 17

&lt;211&gt; 696

&lt;212&gt; DNA

<213> *Neisseria meningitidis*

&lt;400&gt; 17

atgaaactga aaaccttagc ttgacttca ttgacctgt tggcattggc cgctttagc 60  
 aaacaggctg aaaccagtgt tccggcagac agcgcccaaa gcagctcatc tgctccggca 120  
 gccctgctg agttgaacga aggtgtgaac tacactgtat tgtctacgcc tattccgcaa 180  
 cagcaggccg gtaaaatcga agtattggaa ttttccggct acctctgcc gcattgcgcc 240  
 catcttgagc cggctcttag cgagcacatc aaaaagttaa aagacgatac ctatcgcgc 300  
 cgggagcatg tcgtgtgggg tgatgaaatg aaacctttgg cagctttggc ggccgcagtg 360  
 gaaatggccg gtgaatcaga taaagccaac agccatattt tcgatgcgat ggtaatacaa 420  
 aaaatcaatc tggccgatac cgataccctg aaaaaatggc tgtccgagca aacagcgttt 480  
 gacggcaaaa aagtattggc tgcatttgag gctcctgaaa gccaaagcgc tgcggctcaa 540  
 atggaagagt tgaccaataa attccaatc agcggcacac cgactgtgat tgcggcgcg 600  
 aaataccaag ttgaatttaa agactggcag tctggtatga ccacagattga ccagttgggtg 660  
 gataaagtac gcgaagagca gaaaaagccg caataa 696

&lt;210&gt; 18

&lt;211&gt; 231

&lt;212&gt; PRT

<213> *Neisseria meningitidis*

&lt;400&gt; 18

Met Lys Leu Lys Thr Leu Ala Leu Thr Ser Leu Thr Leu Leu Ala Leu  
 1 5 10 15

Ala Ala Cys Ser Lys Gln Ala Glu Thr Ser Val Pro Ala Asp Ser Ala  
 20 25 30

Gln Ser Ser Ser Ser Ala Pro Ala Ala Pro Ala Glu Leu Asn Glu Gly  
 35 40 45

Val Asn Tyr Thr Val Leu Ser Thr Pro Ile Pro Gln Gln Gln Ala Gly  
 50 55 60

Lys Ile Glu Val Leu Glu Phe Phe Gly Tyr Phe Cys Pro His Cys Ala  
 65 70 75 80

His Leu Glu Pro Val Leu Ser Glu His Ile Lys Thr Phe Lys Asp Asp  
85 95

Thr Tyr Met Arg Arg Glu His Val Val Trp Gly Asp Glu Met Lys Pro  
100 105 110

Leu Ala Arg Leu Ala Ala Ala Val Glu Met Ala Gly Glu Ser Asp Lys  
115 120 125

Ala Asn Ser His Ile Phe Asp Ala Met Val Asn Gln Lys Ile Asn Leu  
130 135 140

Ala Asp Thr Asp Thr Leu Lys Lys Trp Leu Ser Glu Gln Thr Ala Phe  
145 150 155 160

Asp Gly Lys Lys Val Leu Ala Ala Phe Glu Ala Pro Glu Ser Gln Ala  
165 170 175

Arg Ala Ala Gln Met Glu Glu Leu Thr Asn Lys Phe Gln Ile Ser Gly  
180 185 190

Thr Pro Thr Val Ile Val Gly Gly Lys Tyr Gln Val Glu Phe Lys Asp  
195 200 205

Trp Gln Ser Gly Met Thr Thr Ile Asp Gln Leu Val Asp Lys Val Arg  
210 215 220

Glu Glu Gln Lys Lys Pro Gln  
225 230

<210> 19

<211> 696

<212> DNA

<213> *Neisseria meningitidis*

<400> 19

atgaaactga aaaccttagc tttgacttca ttgaccctgt tggcattggc gcctttagc 60  
aaacaggctg aaaccagtgt tccggcagac agcgcccaaa gcagctcacg tgctccggca 120  
gccctgctg agttgaacga aggtgtgaac tacactgtat tgtctacgcc tattccgcaa 180  
cagcagcgcc gtaaaatcga agtattggaa ttttctcgct acttctgcc ccattgcgcc 240  
catcttgagc cggctttgag cgagcacatc aaaacgttta aagacgatac ctatatgcgc 300  
cgggagcatg tcgtgtgggg tgatgaaatg aaacctttgg cactttggc ggccgagtg 360  
gaaatggccg gtgaatcaga taaagccaac agccatatt tcgatcgcat ggttaataca 420  
aaaatcaatc tggccgatac cgataccctg aaaaaatggc tgtccgagca aacagcgttt 480  
gacggcaaaa aagtattggc tgcatttgag gctcctgaaa gccaaagcgc tgccgctcaa 540  
atggaagagt tgaccaataa attccaaatc agcggcacac cgactgtgat tgcggcgccg 600



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aaataccaag ttgaatttaa agactggcag tctggtatga ccacgattga ccagttggtg 660  
gataaaqtac qcgaagagca gaaaaagccg caataa 696

<210> 20

<211> 231

&lt;212&gt; PRT

<213> *Neisseria meningitidis*

<400> 20

Met Lys Leu Lys Thr Leu Ala Leu Thr Ser Leu Thr Leu Leu Ala Leu  
1 5 10 15

Ala Ala Cys Ser Lys Gln Ala Glu Thr Ser Val Pro Ala Asp Ser Ala  
20 25 30

Gln Ser Ser Ser Ser Ala Pro Ala Ala Pro Ala Glu Leu Asn Glu Gly  
35 40 45

Val Asn Tyr Thr Val Leu Ser Thr Pro Ile Pro Gln Gln Gln Ala Gly  
50 55 60

Lys Ile Glu Val Leu Glu Phe Phe Gly Tyr Phe Cys Pro His Cys Ala  
65 70 75 80

His Leu Glu Pro Val Leu Ser Glu His Ile Lys Thr Phe Lys Asp Asp  
85 90 95

Thr Tyr Met Arg Arg Glu His Val Val Trp Gly Asp Glu Met Lys Pro  
100 105 110

Leu Ala Arg Leu Ala Ala Ala Val Glu Met Ala Gly Glu Ser Asp Lys  
115 120 125

Ala Asn Ser His Ile Phe Asp Ala Met Val Asn Gln Lys Ile Asn Leu  
130 135 140

Ala Asp Thr Asp Thr Leu Lys Lys Trp Leu Ser Glu Gln Thr Ala Phe  
145 150 155 160

Asp Gly Lys Lys Val Leu Ala Ala Phe Glu Ala Pro Glu Ser Gln Ala  
165 170 175

Arg Ala Ala Gln Met Glu Glu Leu Thr Asn Lys Phe Gln Ile Ser Gly  
180 185 190

Thr Pro Thr Val Ile Val Gly Gly Lys Tyr Gln Val Glu Phe Lys Asp  
195 200 205

Trp Gln Ser Gly Met Thr Thr Ile Asp Gln Leu Val Asp Lys Val Arg  
 210 215 220

Glu Glu Gln Lys Lys Pro Gln  
 225 230

<210> 21  
 <211> 696  
 <212> DNA  
 <213> *Neisseria meningitidis*

<400> 21  
 atgaaactga aaaccttagc ttgacttca ttgacctgt tggcattggc cgcttgtagc 60  
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 gccccagccc cattgaccga aggcgtgaac tacactgtat tgtccacgcc tatcccgcaa 180  
 cagcaggccg gcaaagtcca agtcctggaa ttttctggct acttctgcc gcattgcgcc 240  
 catcttgagc cggctctgag cgagcacatc aaaacgttta aagacgatac ctatatgcgc 300  
 cgggagcatg tcgtgtgggg tgatgaaatg aaacctttgg cacgtttggc ggccgcagtg 360  
 gaaatggcgg gtgaatcaga taaagccaac agccatattt tcgatgcgat ggtaaataca 420  
 aaaatacaatc tggccgatac cgataccctg aaaaaatggc tgtccgagca aacagcgttt 480  
 gacggcaaaa aagtattggc tgcatttgag gcttctgaaa gccaaagcgc tgcggctcaa 540  
 atggaagagt tgaccaataa attccaaatc agcggcacac cgactgtgat cgtcggcgcc 600  
 aaataccaag ttgaatttaa agactggcag tccggtatga ccacgattga ccagtgtgtg 660  
 gataaagtac gcgaagagca gaaaaagccg caataa 696

<210> 22  
 <211> 231  
 <212> PRT  
 <213> *Neisseria meningitidis*

<400> 22  
 Met Lys Leu Lys Thr Leu Ala Leu Thr Ser Leu Thr Leu Leu Ala Leu  
 1 5 10 15

Ala Ala Cys Ser Lys Gln Ala Glu Thr Ser Val Pro Ala Asp Ser Val  
 20 25 30

Gln Ser Ser Ser Ala Pro Ala Ala Pro Ala Pro Leu Thr Glu Gly  
 35 40 45

Val Asn Tyr Thr Val Leu Ser Thr Pro Ile Pro Gln Gln Ala Gly  
 50 55 60

Lys Val Glu Val Leu Glu Phe Phe Gly Tyr Phe Cys Pro His Cys Ala  
 65 70 75 80

His Leu Glu Pro Val Leu Ser Glu His Ile Lys Thr Phe Lys Asp Asp  
85 90 95

Thr Tyr Met Arg Arg Glu His Val Val Trp Gly Asp Glu Met Lys Pro  
100 105 110

Leu Ala Arg Leu Ala Ala Ala Val Glu Met Ala Gly Glu Ser Asp Lys  
115 120 125

Ala Asn Ser His Ile Phe Asp Ala Met Val Asn Gln Lys Ile Asn Leu  
130 135 140

Ala Asp Thr Asp Thr Leu Lys Lys Trp Leu Ser Glu Gln Thr Ala Phe  
145 150 155 160

Asp Gly Lys Lys Val Leu Ala Ala Phe Glu Ala Ser Glu Ser Gln Ala  
165 170 175

Arg Ala Ala Gln Met Glu Glu Leu Thr Asn Lys Phe Gln Ile Ser Gly  
180 185 190

Thr Pro Thr Val Ile Val Gly Gly Lys Tyr Gln Val Glu Phe Lys Asp  
195 200 205

Trp Gln Ser Gly Met Thr Thr Ile Asp Gln Leu Val Asp Lys Val Arg  
210 215 220

Glu Glu Gln Lys Lys Pro Gln  
225 230

<210> 23

<211> 696

<212> DNA

<213> *Neisseria meningitidis*

<400> 23

atgaaactga aaaccttagc ttgacttca ttgaccctgt tggcattggc cgcttgtagc 60  
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gccccagccc cattgaccga aggcgtgaac tacactgtat tgtccacgccc tatcccgcaa 180  
cagcaggccg gcaaatcgca agtcttggaa ttttctggct acctctgccc gcattcgccc 240  
catcttgagc cggctcttgag cgagcacatc aaaacgttta aagacgatac ctatatgcgc 300  
cgggagcatg tcgtgtgggg tgatgaaatg aaacctttgg cagctttggc ggccgcagtg 360  
gaaatggccg gtgaatcaga taaagccaac agccatattt tcgatgcgat ggtaaatcaa 420  
aaaatcaatc tggccgatac cgataccctg aaaaaatggc tgtccgagca aacagcgctt 480  
gacgcaaaaa aagtattggc tgcatttgag gcttctgaaa gccaaagcgc tgccggctcaa 540  
atggaagagt tgaccaataa attccaaatc agcggcacac cgactgtgat cgtcggcgcc 600  
aaataccaag ttgaatttaa agactggcag tccgggtatga ccacgattga ccagttgggtg 660

gataaaagtac gcgaagagca gaaaaagccg caataa

696

&lt;210&gt; 24

&lt;211&gt; 231

&lt;212&gt; PRT

<213> *Neisseria meningitidis*

&lt;400&gt; 24

Met	Lys	Leu	Lys	Thr	Leu	Ala	Leu	Thr	Ser	Leu	Thr	Leu	Leu	Ala	Leu
1				5					10					15	

Ala	Ala	Cys	Ser	Lys	Gln	Ala	Glu	Thr	Ser	Val	Pro	Ala	Asp	Ser	Val
			20					25					30		

Gln	Ser	Ser	Ser	Ser	Ala	Pro	Ala	Ala	Pro	Ala	Pro	Leu	Thr	Glu	Gly
			35					40					45		

Val	Asn	Tyr	Thr	Val	Leu	Ser	Thr	Pro	Ile	Pro	Gln	Gln	Gln	Ala	Gly
			50				55					60			

Lys	Val	Glu	Val	Leu	Glu	Phe	Phe	Gly	Tyr	Phe	Cys	Pro	His	Cys	Ala
	65				70					75					80

His	Leu	Glu	Pro	Val	Leu	Ser	Glu	His	Ile	Lys	Thr	Phe	Lys	Asp	Asp
				85					90					95	

Thr	Tyr	Met	Arg	Arg	Glu	His	Val	Val	Trp	Gly	Asp	Glu	Met	Lys	Pro
			100					105						110	

Leu	Ala	Arg	Leu	Ala	Ala	Ala	Val	Glu	Met	Ala	Gly	Glu	Ser	Asp	Lys
			115				120							125	

Ala	Asn	Ser	His	Ile	Phe	Asp	Ala	Met	Val	Asn	Gln	Lys	Ile	Asn	Leu
	130					135						140			

Ala	Asp	Thr	Asp	Thr	Leu	Lys	Lys	Trp	Leu	Ser	Glu	Gln	Thr	Ala	Phe
	145				150				155					160	

Asp	Gly	Lys	Lys	Val	Leu	Ala	Ala	Phe	Glu	Ala	Ser	Glu	Ser	Gln	Ala
				165					170					175	

Arg	Ala	Ala	Gln	Met	Glu	Glu	Leu	Thr	Asn	Lys	Phe	Gln	Ile	Ser	Gly
			180					185					190		

Thr	Pro	Thr	Val	Ile	Val	Gly	Gly	Lys	Tyr	Gln	Val	Glu	Phe	Lys	Asp
			195				200							205	

Trp	Gln	Ser	Gly	Met	Thr	Thr	Ile	Asp	Gln	Leu	Val	Asp	Lys	Val	Arg
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

210

215

220

Glu Glu Gln Lys Lys Pro Gln  
225 230

&lt;210&gt; 25

&lt;211&gt; 696

&lt;212&gt; DNA

<213> *Neisseria meningitidis*

&lt;400&gt; 25

```

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aaacaggctg aaaccagcgt tccggcagac agcgctccaa gcagctcacc tgctccggca 120
gccccagccc cattgaccga aggcgtgaac tacactgtat tgtccacgcc tatcccgcga 180
cagcaggccg gcaaagtcca agtcttggaa tttttcggct acttctgccc gcattgcgcc 240
catcttgagc cggctcttgag cgagcacatc aaaacgttta aagacgatac ctatatgcgc 300
cgggagcatg tcgtgtgggg tgatgaaatg aaacctttgg cactgttggc ggccgcagtg 360
gaaatggccg gtgaatcaga taaagccaac agccatattt tcgatgcgat gggttaataca 420
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gacggcaaaa aagtattggc tgcatttgag gctcctgaaa gccaaagcgc tgccggctcaa 540
atgggaagagt tgaccaataa attccaaatc agcggcacac cgactgtgat tgcggcgccg 600
aaataccaag tgaatttaa agactggcag tccggtatga ccacgattga ccagttggtg 660
gataaagatc gcgaagagca gaaaaagccg caataa 696

```

&lt;210&gt; 26

&lt;211&gt; 231

&lt;212&gt; PRT

<213> *Neisseria meningitidis*

&lt;400&gt; 26

```

Met Lys Leu Lys Thr Leu Ala Leu Thr Ser Leu Thr Leu Leu Ala Leu
  1                      5                      10                     15

```

```

Ala Ala Cys Ser Lys Gln Ala Glu Thr Ser Val Pro Ala Asp Ser Val
                      20                      25                     30

```

```

Gln Ser Ser Ser Ser Ala Pro Ala Ala Pro Ala Pro Leu Thr Glu Gly
  35                      40                      45

```

```

Val Asn Tyr Thr Val Leu Ser Thr Pro Ile Pro Gln Gln Gln Ala Gly
  50                      55                      60

```

```

Lys Val Glu Val Leu Glu Phe Phe Gly Tyr Phe Cys Pro His Cys Ala
  65                      70                      75                     80

```

```

His Leu Glu Pro Val Leu Ser Glu His Ile Lys Thr Phe Lys Asp Asp
  85                      90                      95

```

Thr Tyr Met Arg Arg Glu His Val Val Trp Gly Asp Glu Met Lys Pro  
 100 105 110

Leu Ala Arg Leu Ala Ala Val Glu Met Ala Gly Glu Ser Asp Lys  
 115 120 125

Ala Asn Ser His Ile Phe Asp Ala Met Val Asn Gln Lys Ile Asn Leu  
 130 135 140

Ala Asp Thr Asp Thr Leu Lys Lys Trp Leu Ser Glu Gln Thr Ala Phe  
 145 150 155 160

Asp Gly Lys Lys Val Leu Ala Ala Phe Glu Ala Pro Glu Ser Gln Ala  
 165 170 175

Arg Ala Ala Gln Met Glu Glu Leu Thr Asn Lys Phe Gln Ile Ser Gly  
 180 185 190

Thr Pro Thr Val Ile Val Gly Gly Lys Tyr Gln Val Glu Phe Lys Asp  
 195 200 205

Trp Gln Ser Gly Met Thr Thr Ile Asp Gln Leu Val Asp Lys Val Arg  
 210 215 220

Glu Glu Gln Lys Lys Pro Gln  
 225 230

<210> 27

<211> 1047

<212> DNA

<213> Neisseria meningitidis

<400> 27

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 gattggggca gcctgaccga acaagaggca aggcagttta tctatttgat tgagaaagat 120  
 cgatattcta atcaattgct tgaccgatat caaaaaaatc caagtagttt aaataatcaa 180  
 gaaaaaata ttcttgcata ttttattaac caaacctctg gaggtaacac agcttgggca 240  
 gcttcgatac tgaaaaacgc ccagtcfaatg ggtaattcca ctattccttc caaagatatt 300  
 aataacacct tatcgaaagc ctatcaaaaca ttgagtcggt atgattcttt tgattacaaa 360  
 tcagctgttg ccgcacaacc tgcactttac ttattaaacg gaccgcttgg cttcagtgctc 420  
 aaagcagcta ctgtggcagc aggaggatat aacattggac agggagcgaa agcaatctct 480  
 aatggagaat atctgcatgg tacagttcag gttgttaatg gcacattgat ggttgaggga 540  
 tctgtatctg cacaggctgc aatatcgccc aagcctgcac ctgttaccgg ttaattctgagc 600  
 aatgacagtg ctccctgctt aagacaagct ttaactgctg aaagccagag aatccgcgatg 660  
 aaactgcggg aagagtatcg acaaataggg aatcttgcca tagcaaaaat tgatgttaaa 720  
 ggattaccgc aaaggatgga agcatttagt tctttccaaa aaggggaaca tggatttatt 780

```

tcgttacctg aaacaaaaat ttttaaacct atatctgttg ataatatca taatattgcc 840
tctcctccta gaggaacatt aagaaatata gatggagaat ataaattact tgaactata 900
gcacagcaac tcggaataaa tcgtaatgta tcaggtagaa tgcgtctatt tacagaatta 960
aaggcctgtc aatcttcgag caatgttatt ttagagtta gaaatcgcta tccaaatatt 1020
caattaaata tttttacagg aaaatag 1047

```

&lt;210&gt; 28

&lt;211&gt; 348

&lt;212&gt; PRT

&lt;213&gt; Neisseria meningitidis

&lt;400&gt; 28

```

Glu Tyr Ala Leu Arg Glu Lys Leu Ile Lys Lys Ala Lys Gly Lys Gly
  1                      5                      10                      15

```

```

Leu Leu Ser Leu Asp Trp Gly Ser Leu Thr Glu Gln Glu Ala Arg Gln
                20                      25                      30

```

```

Phe Ile Tyr Leu Ile Glu Lys Asp Arg Tyr Ser Asn Gln Leu Leu Asp
  35                      40                      45

```

```

Arg Tyr Gln Lys Asn Pro Ser Ser Leu Asn Asn Gln Glu Lys Asn Ile
  50                      55                      60

```

```

Leu Ala Tyr Phe Ile Asn Gln Thr Ser Gly Gly Asn Thr Ala Trp Ala
  65                      70                      75                      80

```

```

Ala Ser Ile Leu Lys Thr Pro Gln Ser Met Gly Asn Leu Thr Ile Pro
                85                      90                      95

```

```

Ser Lys Asp Ile Asn Asn Thr Leu Ser Lys Ala Tyr Gln Thr Leu Ser
  100                      105                      110

```

```

Arg Tyr Asp Ser Phe Asp Tyr Lys Ser Ala Val Ala Ala Gln Pro Ala
  115                      120                      125

```

```

Leu Tyr Leu Leu Asn Gly Pro Leu Gly Phe Ser Val Lys Ala Ala Thr
  130                      135                      140

```

```

Val Ala Ala Gly Gly Tyr Asn Ile Gly Gln Gly Ala Lys Ala Ile Ser
  145                      150                      155                      160

```

```

Asn Gly Glu Tyr Leu His Gly Thr Val Gln Val Val Asn Gly Thr Leu
                165                      170                      175

```

```

Met Val Ala Gly Ser Val Ser Ala Gln Ala Ala Ile Ser Ala Lys Pro
                180                      185                      190

```

Ala Pro Val Thr Arg Tyr Leu Ser Asn Asp Ser Ala Pro Ala Leu Arg  
195 200 205

Gln Ala Leu Thr Ala Glu Ser Gln Arg Ile Arg Met Lys Leu Pro Glu  
210 215 220

Glu Tyr Arg Gln Ile Gly Asn Leu Ala Ile Ala Lys Ile Asp Val Lys  
225 230 235 240

Gly Leu Pro Gln Arg Met Glu Ala Phe Ser Ser Phe Gln Lys Gly Glu  
245 250 255

His Gly Phe Ile Ser Leu Pro Glu Thr Lys Ile Phe Lys Pro Ile Ser  
260 265 270

Val Asp Lys Tyr His Asn Ile Ala Ser Pro Pro Arg Gly Thr Leu Arg  
275 280 285

Asn Ile Asp Gly Glu Tyr Lys Leu Leu Glu Thr Ile Ala Gln Gln Leu  
290 295 300

Gly Asn Asn Arg Asn Val Ser Gly Arg Ile Asp Leu Phe Thr Glu Leu  
305 310 315 320

Lys Ala Cys Gln Ser Cys Ser Asn Val Ile Leu Glu Phe Arg Asn Arg  
325 330 335

Tyr Pro Asn Ile Gln Leu Asn Ile Phe Thr Gly Lys  
340 345

<210> 29

<211> 2112

<212> DNA

<213> Neisseria meningitidis

<400> 29

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gctgccgccg atacgcagga caatggtgaa cattacaccg ccactctgcc caccgtttcc 120  
gtggctcgagc agtccgacac cagcgtactc aaaggctaca tcaactacga cgaagccgcc 180  
gttaccgcga acggacagct catcaaaaga acgccgcaaa ccatcgatac gctcaatata 240  
cagaaaaaca aaaattacgg cagcaacgat ttgagttcca tcctcgaagg caatgccggc 300  
atcgacgccg cctacgatat gcgcggcgaa agcattttcc tgcgcggctt tcaagccgac 360  
gcattctgata ttaccgcga cggcgtacgc gaaagcgggc aggtgcgccg tagcaccgcc 420  
aacatcgagc gcgtggaat cctgaaaggc ccgtcctccg tgccttatgg gcgtaccaac 480  
ggcggcggtg tcatcaacat ggtcagcaaa tacgccaaact tcaaaaaaag ccgtaataatc 540  
ggtacgggtt atggttcgtg ggcaaacgc agcctgaata tggacatcaa cgaagtgtg 600  
aacaaaaacg tcgccatccg tctcaccggc gaagtcgggc gcgccaatc gttccgcagc 660



```

ggcatagaca gcaaaaatgt catggtttcg cccagcatta ccgtcaaact cgacaacggc 720
ttgaagtggg cggggcaata cacctacgac aatgtggagc gcacgccga cgcagtcgcg 780
accaagtccg tgtacgaccg cttcggactg ccttaccgca tggggttcgc ccaccggaac 840
gattttgtca aagacaaagt gcaagtttgg cgttcgcgacc ttgaatacgc cttcaacgac 900
aaatggcgctg cccaatggca gctcggccac cgcacggcgg cgcaggattt tgatcatttc 960
tatcgaggca gcgaaaatgg caacttaatc aaacgttaact acgcctggca gcagaccgac 1020
aacaaaaacc tgcgttccaa cttaacgctc aacggcgact acaccatcgg ccgttttgaa 1080
aaccacctga ccgtaggcat ggattacagc cgcgaacacc gcaacccgac attgggtttc 1140
agcagcgctt tttccgcctc catcaacccc tacgaccgcg caagtggccg ggcttcgggc 1200
agattgcgac ctattctgac ccaaaacggc cacaagcgcg actcctacgg catctttgtg 1260
caaaacatct tctccgcac gcccgatttg aaattcgtcc tcggcgccgc ttacgacaaa 1320
tacaccttta attccgaaaa caaactcacc ggcagcagcc gccaatagag cggacactcg 1380
ttcagcccca acatcggcgc agtggtgaac atcaatcccg tccacacact ttacgcctcg 1440
tataacaaag gcttcgcgcc ttatggcgga cgcggcgctt attgagcat cgatcgttg 1500
tcttccgcgc tgttcaacgc cgaccccgag tacacccgcc aatacgaac cggcgtgaaa 1560
agcagttggc tggacgacgc cctcagcact acgttgtctg cctaccaaat cgaacgcttc 1620
aatatccgct accgcccga tccaaaaaac aacccttata ttatcggtt tagcggcaaa 1680
cacggttcgc gcggcggtga attgtccgcc atcggggaaa tcactcccaa aaaactctat 1740
ctgcgcggtt cgtttggcgt gatgcaggcg aagatcggtt aagacaaaaga aatcccgac 1800
cgagtgggca tccatttgaa taacaccagc aacgttaccg gcaacctgtt ttccggttat 1860
accccgacgc aaaaacctta cggcgaaatc ggcgtaaccg gtacaggcaa acgctacggt 1920
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cttggtcgga accataaaaa tgttaacggt acctttgccg cagccaatct gttcaatcaa 2040
aaatatggc gttcggactc tatgcgggtt aatccgcgcg gctatactgc ccgggtaaat 2100
taccgtttct ga 2112

```

&lt;210&gt; 30

&lt;211&gt; 703

&lt;212&gt; PRT

<213> *Neisseria meningitidis*

&lt;400&gt; 30

```

Met Lys Ile Ser Phe His Leu Ala Leu Leu Pro Thr Leu Ile Ile Ala
  1             5             10             15

```

```

Ser Phe Pro Val Ala Ala Ala Asp Thr Gln Asp Asn Gly Glu His Tyr
          20             25             30

```

```

Thr Ala Thr Leu Pro Thr Val Ser Val Val Gly Gln Ser Asp Thr Ser
          35             40             45

```

```

Val Leu Lys Gly Tyr Ile Asn Tyr Asp Glu Ala Ala Val Thr Arg Asn
          50             55             60

```

```

Gly Gln Leu Ile Lys Glu Thr Pro Gln Thr Ile Asp Thr Leu Asn Ile
          65             70             75             80

```

```

Gln Lys Asn Lys Asn Tyr Gly Thr Asn Asp Leu Ser Ser Ile Leu Glu

```

	85		90		95
Gly Asn Ala Gly Ile Asp Ala Ala Tyr Asp Met Arg Gly Glu Ser Ile	100		105		110
Phe Leu Arg Gly Phe Gln Ala Asp Ala Ser Asp Ile Tyr Arg Asp Gly	115		120		125
Val Arg Glu Ser Gly Gln Val Arg Arg Ser Thr Ala Asn Ile Glu Arg	130		135		140
Val Glu Ile Leu Lys Gly Pro Ser Ser Val Leu Tyr Gly Arg Thr Asn	145		150		155
					160
Gly Gly Gly Val Ile Asn Met Val Ser Lys Tyr Ala Asn Phe Lys Gln	165		170		175
Ser Arg Asn Ile Gly Thr Val Tyr Gly Ser Trp Ala Asn Arg Ser Leu	180		185		190
Asn Met Asp Ile Asn Glu Val Leu Asn Lys Asn Val Ala Ile Arg Leu	195		200		205
Thr Gly Glu Val Gly Arg Ala Asn Ser Phe Arg Ser Gly Ile Asp Ser	210		215		220
Lys Asn Val Met Val Ser Pro Ser Ile Thr Val Lys Leu Asp Asn Gly	225		230		235
					240
Leu Lys Trp Thr Gly Gln Tyr Thr Tyr Asp Asn Val Glu Arg Thr Pro	245		250		255
Asp Arg Ser Pro Thr Lys Ser Val Tyr Asp Arg Phe Gly Leu Pro Tyr	260		265		270
Arg Met Gly Phe Ala His Arg Asn Asp Phe Val Lys Asp Lys Leu Gln	275		280		285
Val Trp Arg Ser Asp Leu Glu Tyr Ala Phe Asn Asp Lys Trp Arg Ala	290		295		300
Gln Trp Gln Leu Ala His Arg Thr Ala Ala Gln Asp Phe Asp His Phe	305		310		315
					320
Tyr Ala Gly Ser Glu Asn Gly Asn Leu Ile Lys Arg Asn Tyr Ala Trp	325		330		335
Gln Gln Thr Asp Asn Lys Thr Leu Ser Ser Asn Leu Thr Leu Asn Gly					

340	345	350
Asp Tyr Thr Ile Gly Arg Phe Glu Asn His Leu Thr Val Gly Met Asp		
355	360	365
Tyr Ser Arg Glu His Arg Asn Pro Thr Leu Gly Phe Ser Ser Ala Phe		
370	375	380
Ser Ala Ser Ile Asn Pro Tyr Asp Arg Ala Ser Trp Pro Ala Ser Gly		
385	390	400
Arg Leu Gln Pro Ile Leu Thr Gln Asn Arg His Lys Ala Asp Ser Tyr		
405	410	415
Gly Ile Phe Val Gln Asn Ile Phe Ser Ala Thr Pro Asp Leu Lys Phe		
420	425	430
Val Leu Gly Gly Arg Tyr Asp Lys Tyr Thr Phe Asn Ser Glu Asn Lys		
435	440	445
Leu Thr Gly Ser Ser Arg Gln Tyr Ser Gly His Ser Phe Ser Pro Asn		
450	455	460
Ile Gly Ala Val Trp Asn Ile Asn Pro Val His Thr Leu Tyr Ala Ser		
465	470	480
Tyr Asn Lys Gly Phe Ala Pro Tyr Gly Gly Arg Gly Gly Tyr Leu Ser		
485	490	495
Ile Asp Thr Leu Ser Ser Ala Val Phe Asn Ala Asp Pro Glu Tyr Thr		
500	505	510
Arg Gln Tyr Glu Thr Gly Val Lys Ser Ser Trp Leu Asp Asp Arg Leu		
515	520	525
Ser Thr Thr Leu Ser Ala Tyr Gln Ile Glu Arg Phe Asn Ile Arg Tyr		
530	535	540
Arg Pro Asp Pro Lys Asn Asn Pro Tyr Ile Tyr Ala Val Ser Gly Lys		
545	550	555
His Arg Ser Arg Gly Val Glu Leu Ser Ala Ile Gly Gln Ile Ile Pro		
565	570	575
Lys Lys Leu Tyr Leu Arg Gly Ser Leu Gly Val Met Gln Ala Lys Val		
580	585	590
Val Glu Asp Lys Glu Asn Pro Asp Arg Val Gly Ile His Leu Asn Asn		

595

600

605

Thr Ser Asn Val Thr Gly Asn Leu Phe Phe Arg Tyr Thr Pro Thr Glu  
610 615 620

Asn Leu Tyr Gly Glu Ile Gly Val Thr Gly Thr Gly Lys Arg Tyr Gly  
625 630 635 640

Tyr Asp Ser Arg Asn Lys Glu Val Thr Thr Leu Pro Gly Phe Ala Arg  
645 650 655

Val Asp Ala Met Leu Gly Trp Asn His Lys Asn Val Asn Val Thr Phe  
660 665 670

Ala Ala Ala Asn Leu Phe Asn Gln Lys Tyr Trp Arg Ser Asp Ser Met  
675 680 685

Pro Gly Asn Pro Arg Gly Tyr Thr Ala Arg Val Asn Tyr Arg Phe  
690 695 700

&lt;210&gt; 31

&lt;211&gt; 2113

&lt;212&gt; DNA

<213> *Neisseria meningitidis*

&lt;400&gt; 31

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gtggtcggag agtccgacac cagcgtactc aaaggtacata tcaactacga cgaagccgcc 180  
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cagaaaaaca aaaattacgg caggaacgat ttgagttcca tctcgaagg caatgcggcg 300  
atcgacgcgc cctacgatat gcgcggcgaa agcattttcc tgcgcggctt tcaagccgac 360  
gcattctgata ttaccgcga cggcgtagc gaaagcgggc aggtgcgcgc tagcaccgcc 420  
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aacaataaac tcgccatccg tctcaccggc gaagtccggc gcgccaatc gttccgcagc 660  
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agcagcgctt ttccgcctc catcaacccc tacgaccgag caagctggcc ggcttcgggc 1200  
agattgcagc ctattctgac ccaaaaccgc cacaagccg actcctacgc catctttgtg 1260

```

caaaacatct tctccgccac gcccgatttg aaattcgtcc tcggcggccg ttacgacaaa 1320
tacaccttta attccgaaaa caaactcacc ggcagcagcc gccaatcacg cggacactcg 1380
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aaaatatggc cgttcggact ctatgccggg taatccgcgc ggctatactg cccgggtaaa 2100
ttaccgtttc tga 2113

```

&lt;210&gt; 32

&lt;211&gt; 697

&lt;212&gt; PRT

<213> *Neisseria meningitidis*

&lt;400&gt; 32

```

Met Lys Ile Ser Phe His Leu Ala Leu Leu Pro Thr Leu Ile Ile Ala
  1             5             10             15

```

```

Ser Phe Pro Val Ala Ala Ala Asp Thr Gln Asp Asn Gly Glu His Tyr
      20             25             30

```

```

Thr Ala Thr Leu Pro Thr Val Ser Val Val Gly Gln Ser Asp Thr Ser
      35             40             45

```

```

Val Leu Lys Gly Tyr Ile Asn Tyr Asp Glu Ala Ala Val Thr Arg Asn
      50             55             60

```

```

Gly Gln Leu Ile Lys Glu Thr Pro Gln Thr Ile Asp Thr Leu Asn Ile
      65             70             75             80

```

```

Gln Lys Asn Lys Asn Tyr Gly Thr Asn Asp Leu Ser Ser Ile Leu Glu
      85             90             95

```

```

Gly Asn Ala Gly Ile Asp Ala Ala Tyr Asp Met Arg Gly Glu Ser Ile
      100             105             110

```

```

Phe Leu Arg Gly Phe Gln Ala Asp Ala Ser Asp Ile Tyr Arg Asp Gly
      115             120             125

```

```

Val Arg Glu Ser Gly Gln Val Arg Arg Ser Thr Ala Asn Ile Glu Arg
      130             135             140

```

Val Glu Ile Leu Lys Gly Pro Ser Ser Val Leu Tyr Gly Arg Thr Asn  
145 150 155 160

Gly Gly Gly Val Ile Asn Met Val Ser Lys Tyr Ala Asn Phe Lys Gln  
165 170 175

Ser Arg Asn Ile Gly Thr Val Tyr Gly Ser Trp Ala Asn Arg Ser Leu  
180 185 190

Asn Met Asp Ile Asn Glu Val Leu Asn Lys Asn Val Ala Ile Arg Leu  
195 200 205

Thr Gly Glu Val Gly Arg Ala Asn Ser Phe Arg Ser Gly Ile Asp Ser  
210 215 220

Lys Asn Val Met Val Ser Pro Ser Ile Thr Val Lys Leu Asp Asn Gly  
225 230 235 240

Leu Lys Trp Thr Gly Gln Tyr Thr Tyr Asp Asn Val Glu Arg Thr Pro  
245 250 255

Asp Arg Ser Pro Thr Lys Ser Val Tyr Asp Arg Phe Gly Leu Pro Tyr  
260 265 270

Arg Met Gly Phe Ala His Arg Asn Asp Phe Val Lys Asp Lys Leu Gln  
275 280 285

Val Trp Arg Ser Asp Leu Glu Tyr Ala Phe Asn Asp Lys Trp Arg Ala  
290 295 300

Gln Trp Gln Leu Ala His Arg Thr Ala Ala Gln Asp Phe Asp His Phe  
305 310 315 320

Tyr Ala Gly Ser Glu Asn Gly Asn Leu Ile Lys Arg Asn Tyr Ala Trp  
325 330 335

Gln Gln Thr Asp Asn Lys Thr Leu Ser Ser Asn Leu Thr Leu Asn Gly  
340 345 350

Asp Tyr Thr Ile Gly Arg Phe Glu Asn His Leu Thr Val Gly Met Asp  
355 360 365

Tyr Ser Arg Glu His Arg Asn Pro Thr Leu Gly Phe Ser Ser Ala Phe  
370 375 380

Ser Ala Ser Ile Asn Pro Tyr Asp Arg Ala Ser Trp Pro Ala Ser Gly  
385 390 395 400

Arg Leu Gln Pro Ile Leu Thr Gln Asn Arg His Lys Ala Asp Ser Tyr  
 405 410 415

Gly Ile Phe Val Gln Asn Ile Phe Ser Ala Thr Pro Asp Leu Lys Phe  
 420 425 430

Val Leu Gly Gly Arg Tyr Asp Lys Tyr Thr Phe Asn Ser Glu Asn Lys  
 435 440 445

Leu Thr Gly Ser Ser Arg Gln Tyr Ser Gly His Ser Phe Ser Pro Asn  
 450 455 460

Ile Gly Ala Val Trp Asn Ile Asn Pro Val His Thr Leu Tyr Ala Ser  
 465 470 475 480

Tyr Asn Lys Gly Phe Ala Pro Tyr Gly Gly Arg Gly Gly Tyr Leu Ser  
 485 490 495

Ile Asp Thr Leu Ser Ser Ala Val Phe Asn Ala Asp Pro Glu Tyr Thr  
 500 505 510

Arg Gln Tyr Glu Thr Gly Val Lys Ser Ser Trp Leu Asp Asp Arg Leu  
 515 520 525

Ser Thr Thr Leu Ser Ala Tyr Gln Ile Glu Arg Phe Asn Ile Arg Tyr  
 530 535 540

Arg Pro Asp Pro Lys Asn Asn Pro Tyr Ile Tyr Ala Val Ser Gly Lys  
 545 550 555 560

His Arg Ser Arg Gly Val Glu Leu Ser Ala Ile Gly Gln Ile Ile Pro  
 565 570 575

Lys Lys Thr Leu Ser Ala Arg Phe Val Gly Arg Asp Ala Gly Glu Ser  
 580 585 590

Arg Arg Gln Arg Lys Ser Arg Pro Ser Gly His Pro Phe Glu His Gln  
 595 600 605

Gln Arg Tyr Arg Gln Pro Val Phe Pro Leu Tyr Pro Asp Arg Lys Pro  
 610 615 620

Leu Arg Arg Asn Arg Arg Asn Arg Tyr Arg Gln Thr Leu Arg Leu Arg  
 625 630 635 640

Leu Lys Lys Arg Ser Asp Tyr Ala Ser Arg Leu Cys Pro Ser Cys His  
 645 650 655

WO 01/04150

PCT/EP00/06943

Ala Trp Leu Glu Pro Lys Cys Arg Tyr Leu Cys Arg Ser Gln Ser Val  
660 665 670

Gln Ser Lys Ile Leu Ala Phe Gly Leu Tyr Ala Gly Ser Ala Arg Leu  
675 680 685

Tyr Cys Pro Gly Lys Leu Pro Phe Leu  
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<210> 33

<211> 2111

<212> DNA

<213> *Neisseria meningitidis*

<400> 33

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<210> 34  
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 <212> PRT  
 <213> Neisseria meningitidis

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 Thr Ala Thr Leu Pro Thr Val Ser Val Val Gly Gln Ser Asp Thr Ser  
 35 40 45  
 Val Leu Lys Gly Tyr Ile Asn Tyr Asp Glu Ala Ala Val Thr Arg Asn  
 50 55 60  
 Gly Gln Leu Ile Lys Glu Thr Pro Gln Thr Ile Asp Thr Leu Asn Ile  
 65 70 75 80  
 Gln Lys Asn Lys Asn Tyr Gly Thr Asn Asp Leu Ser Ser Ile Leu Glu  
 85 90 95  
 Gly Asn Ala Gly Ile Asp Ala Ala Tyr Asp Met Arg Gly Glu Ser Ile  
 100 105 110  
 Phe Leu Arg Gly Phe Gln Ala Asp Ala Ser Asp Ile Tyr Arg Asp Gly  
 115 120 125  
 Val Arg Glu Ser Gly Gln Val Arg Arg Ser Thr Ala Asn Ile Glu Arg  
 130 135 140  
 Val Glu Ile Leu Lys Gly Pro Ser Ser Val Leu Tyr Gly Arg Thr Asn  
 145 150 155 160  
 Gly Gly Gly Val Ile Asn Met Val Ser Lys Tyr Ala Asn Phe Lys Gln  
 165 170 175  
 Ser Arg Asn Ile Gly Ala Val Tyr Gly Ser Arg Ala Asn Arg Ser Leu  
 180 185 190

Val Leu Gly Gly Arg Tyr Asp Lys Tyr Thr Phe Asn Ser Glu Asn Lys  
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WO 01/04150

PCT/EP00/06943

<210> 35

<211> 2112

<212> DNA

<213> *Neisseria meningitidis*

<400> 35

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<210> 36

<211> 703

<212> PRT

<213> *Neisseria meningitidis*

&lt;400&gt; 36

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 20 25 30

Thr Ala Thr Leu Pro Thr Val Ser Val Val Gly Gln Ser Asp Thr Ser  
 35 40 45

Val Leu Lys Gly Tyr Ile Asn Tyr Asp Glu Ala Ala Val Thr Arg Asn  
 50 55 60

Gly Gln Leu Ile Lys Glu Thr Pro Gln Thr Ile Asp Thr Leu Asn Ile  
 65 70 75 80

Gln Lys Asn Lys Asn Tyr Gly Thr Asn Asp Leu Ser Ser Ile Leu Glu  
 85 90 95

Gly Asn Ala Gly Ile Asp Ala Ala Tyr Asp Met Arg Gly Glu Ser Ile  
 100 105 110

Phe Leu Arg Gly Phe Gln Ala Asp Ala Ser Asp Ile Tyr Arg Asp Gly  
 115 120 125

Val Arg Glu Ser Gly Gln Val Arg Arg Ser Thr Ala Asn Ile Glu Arg  
 130 135 140

Val Glu Ile Leu Lys Gly Pro Ser Ser Val Leu Tyr Gly Arg Thr Asn  
 145 150 155 160

Gly Gly Gly Val Ile Asn Met Val Ser Lys Tyr Ala Asn Phe Lys Gln  
 165 170 175

Ser Arg Asn Ile Gly Ala Val Tyr Gly Ser Trp Ala Asn Arg Ser Leu  
 180 185 190

Asn Met Asp Ile Asn Glu Val Leu Asn Lys Asn Val Ala Ile Arg Leu  
 195 200 205

Thr Gly Glu Val Gly Arg Ala Asn Ser Phe Arg Ser Gly Ile Asp Ser  
 210 215 220

Lys Asn Val Met Val Ser Pro Ser Ile Thr Val Lys Leu Asp Asn Gly  
 225 230 235 240

Leu Lys Trp Thr Gly Gln Tyr Thr Tyr Asp Asn Val Glu Arg Thr Pro

245

250

255

Asp Arg Ser Pro Thr Lys Ser Val Tyr Asp Arg Phe Gly Leu Pro Tyr  
 260 265 270

Arg Met Gly Phe Ala His Arg Asn Asp Phe Val Lys Asp Lys Leu Gln  
 275 280 285

Val Trp Arg Ser Asp Leu Glu Tyr Ala Phe Asn Asp Lys Trp Arg Ala  
 290 295 300

Gln Trp Gln Leu Ala His Arg Thr Ala Ala Gln Asp Phe Asp His Phe  
 305 310 315 320

Tyr Ala Gly Ser Glu Asn Gly Asn Leu Ile Lys Arg Asn Tyr Ala Trp  
 325 330 335

Gln Gln Thr Asp Asn Lys Thr Leu Ser Ser Asn Leu Thr Leu Asn Gly  
 340 345 350

Asp Tyr Thr Ile Gly Arg Phe Glu Asn His Leu Thr Val Gly Met Asp  
 355 360 365

Tyr Ser Arg Glu His Arg Asn Pro Thr Leu Gly Phe Ser Ser Ala Phe  
 370 375 380

Ser Ala Ser Ile Asn Pro Tyr Asp Arg Ala Ser Trp Pro Ala Ser Gly  
 385 390 395 400

Arg Leu Gln Pro Ile Leu Thr Gln Asn Arg His Lys Ala Asp Ala Tyr  
 405 410 415

Gly Ile Phe Val Gln Asn Ile Phe Ser Ala Thr Pro Asp Leu Lys Phe  
 420 425 430

Val Leu Gly Gly Arg Tyr Asp Lys Tyr Thr Phe Asn Ser Glu Asn Lys  
 435 440 445

Leu Thr Gly Ser Ser Arg Gln Tyr Ser Gly His Ser Phe Ser Pro Asn  
 450 455 460

Ile Gly Ala Val Trp Asn Ile Asn Pro Val His Thr Leu Tyr Ala Ser  
 465 470 475 480

Tyr Asn Lys Gly Phe Ala Pro Tyr Gly Gly Arg Gly Gly Tyr Leu Ser  
 485 490 495

Ile Asn Thr Ser Ser Ser Ala Val Phe Asn Ala Asp Pro Glu Tyr Thr

37

WO 01/04150

PCT/EP00/06943

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&lt;210&gt; 38

&lt;211&gt; 702

&lt;212&gt; PRT

&lt;213&gt; Neisseria meningitidis

&lt;400&gt; 38

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Ser Phe Pro Val Ala Ala Ala Asp Thr Gln Asp Asn Gly Glu His Tyr  
20 25 30

Thr Ala Thr Leu Pro Thr Val Ser Val Val Gly Gln Ser Asp Thr Ser  
35 40 45



Val Leu Lys Gly Tyr Ile Asn Tyr Asp Glu Ala Ala Val Thr Arg Asn  
 50 55 60

Gly Gln Leu Ile Lys Glu Thr Pro Gln Thr Ile Asp Thr Leu Asn Ile  
 65 70 75 80

Lys Asn Lys Asn Tyr Gly Thr Asn Asp Leu Ser Ser Ile Leu Glu Gly  
 85 90 95

Asn Ala Gly Ile Asp Ala Ala Tyr Asp Met Arg Gly Glu Ser Ile Phe  
 100 105 110

Leu Arg Gly Phe Gln Ala Asp Ala Ser Asp Ile Tyr Arg Asp Gly Val  
 115 120 125

Arg Glu Ser Gly Gln Val Arg Arg Ser Thr Ala Asn Ile Glu Arg Val  
 130 135 140

Glu Ile Leu Lys Gly Pro Ser Ser Val Leu Tyr Gly Arg Thr Asn Gly  
 145 150 155 160

Gly Gly Val Ile Asn Met Val Ser Lys Tyr Ala Asn Phe Lys Gln Ser  
 165 170 175

Arg Asn Ile Gly Ala Val Tyr Gly Ser Trp Ala Asn Arg Ser Leu Asn  
 180 185 190

Met Asp Ile Asn Glu Val Leu Asn Lys Asn Val Ala Ile Arg Leu Thr  
 195 200 205

Gly Glu Val Gly Arg Ala Asn Ser Phe Arg Ser Gly Ile Asp Ser Lys  
 210 215 220

Asn Val Met Val Ser Pro Ser Ile Thr Val Lys Leu Asp Asn Gly Leu  
 225 230 235 240

Lys Trp Thr Gly Gln Tyr Thr Tyr Asp Asn Val Glu Arg Thr Pro Asp  
 245 250 255

Arg Ser Pro Thr Lys Ser Val Tyr Asp Arg Phe Gly Leu Pro Tyr Arg  
 260 265 270

Met Gly Phe Ala His Arg Asn Asp Phe Val Lys Asp Lys Leu Gln Val  
 275 280 285

Trp Arg Ser Asp Leu Glu Tyr Ala Phe Asn Asp Lys Trp Arg Ala Gln  
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Trp Gln Leu Ala His Arg Thr Ala Ala Gln Asp Phe Asp His Phe Tyr  
305 310 315 320

Ala Gly Ser Glu Asn Gly Asn Leu Ile Lys Arg Asn Tyr Ala Trp Gln  
325 330 335

Gln Thr Asp Asn Lys Thr Leu Ser Asn Phe Thr Leu Asn Gly Asp  
340 345 350

Tyr Thr Ile Gly Arg Phe Glu Asn His Leu Thr Val Gly Met Asp Tyr  
355 360 365

Ser Arg Glu His Arg Asn Pro Thr Leu Gly Tyr Ser Arg Ala Phe Thr  
370 375 380

Ala Ser Ile Asp Pro Tyr Asp Arg Ala Ser Trp Pro Ala Ser Gly Arg  
385 390 395 400

Leu Gln Pro Ile Leu Thr Gln Asn Arg His Lys Ala Asp Ser Tyr Gly  
405 410 415

Ile Phe Val Gln Asn Ile Phe Ser Ala Thr Pro Asp Leu Lys Phe Val  
420 425 430

Leu Gly Gly Arg Tyr Asp Lys Tyr Thr Phe Asn Ser Glu Asn Lys Leu  
435 440 445

Thr Gly Ser Ser Arg Gln Tyr Ser Gly His Ser Phe Ser Pro Asn Ile  
450 455 460

Gly Ala Val Trp Asn Ile Asn Pro Val His Thr Leu Tyr Ala Ser Tyr  
465 470 475 480

Asn Lys Gly Phe Ala Pro Tyr Gly Gly Arg Gly Gly Tyr Leu Ser Ile  
485 490 495

Asn Thr Ser Ser Ser Ala Val Phe Asn Ala Asp Pro Glu Tyr Thr Arg  
500 505 510

Gln Tyr Glu Thr Gly Val Lys Ser Ser Trp Leu Asp Asp Arg Leu Ser  
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Thr Thr Leu Ser Ala Tyr Gln Ile Glu Arg Phe Asn Ile Arg Tyr Arg  
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Pro Asp Glu Gln Asn Asp Pro Tyr Thr Trp Ala Val Gly Gly Lys His  
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Arg Ser Arg Gly Val Glu Leu Ser Ala Ile Gly Gln Ile Ile Pro Lys  
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Lys Leu Tyr Leu Arg Gly Ser Leu Gly Val Met Gln Ala Lys Val Val  
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Glu Asp Lys Glu Asn Pro Asp Arg Val Gly Ile His Leu Asn Asn Thr  
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Ser Asn Val Thr Gly Asn Leu Phe Phe Arg Tyr Thr Pro Thr Glu Asn  
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Leu Tyr Gly Glu Ile Gly Val Thr Gly Thr Gly Lys Arg Tyr Gly Tyr  
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Asn Ser Arg Asn Lys Glu Val Thr Thr Leu Pro Gly Phe Ala Arg Val  
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Asp Ala Met Leu Gly Trp Asn His Lys Asn Val Asn Ile Thr Phe Ala  
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<211> 2112

<212> DNA

<213> Neisseria meningitidis

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&lt;210&gt; 40

&lt;211&gt; 702

&lt;212&gt; PRT

&lt;213&gt; Neisseria meningitidis

&lt;400&gt; 40

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Met Lys Ile Ser Phe His Leu Ala Leu Leu Pro Thr Leu Ile Ala
1 5 10 15

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Ser Phe Pro Val Ala Ala Ala Asp Thr Gln Asp Asn Gly Glu His Tyr
20 25 30

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Thr Ala Thr Leu Pro Thr Val Ser Val Val Gly Gln Ser Asp Thr Ser
35 40 45

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Val Leu Lys Gly Tyr Ile Asn Tyr Asp Glu Ala Ala Val Thr Arg Asn
50 55 60

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Gly Gln Leu Ile Lys Glu Thr Pro Gln Thr Ile Asp Thr Leu Asn Ile
65 70 75 80

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Lys Asn Lys Asn Tyr Gly Thr Asn Asp Leu Ser Ser Ile Leu Glu Gly
85 90 95

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Asn Ala Gly Ile Asp Ala Ala Tyr Asp Met Arg Gly Glu Ser Ile Phe  
 100 105 110

Leu Arg Gly Phe Gln Ala Asp Ala Ser Asp Ile Tyr Arg Asp Gly Val  
 115 120 125

Arg Glu Ser Gly Gln Val Arg Arg Ser Thr Ala Asn Ile Glu Arg Val  
 130 135 140

Glu Ile Leu Lys Gly Pro Ser Ser Val Leu Tyr Gly Arg Thr Asn Gly  
 145 150 155 160

Gly Gly Val Ile Asn Met Val Ser Lys Tyr Ala Asn Phe Lys Gln Ser  
 165 170 175

Arg Asn Ile Gly Ala Val Tyr Gly Ser Trp Ala Asn Arg Ser Leu Asn  
 180 185 190

Met Asp Ile Asn Glu Val Leu Asn Lys Asn Val Ala Ile Arg Leu Thr  
 195 200 205

Gly Glu Val Gly Arg Ala Asn Ser Phe Arg Ser Gly Ile Asp Ser Lys  
 210 215 220

Asn Val Met Val Ser Pro Ser Ile Thr Val Lys Leu Asp Asn Gly Leu  
 225 230 235 240

Lys Trp Thr Gly Gln Tyr Thr Tyr Asp Asn Val Glu Arg Thr Pro Asp  
 245 250 255

Arg Ser Pro Thr Lys Ser Val Tyr Asp Arg Phe Gly Leu Pro Tyr Arg  
 260 265 270

Met Gly Phe Ala His Arg Asn Asp Phe Val Lys Asp Lys Leu Gln Val  
 275 280 285

Trp Arg Ser Asp Leu Glu Tyr Ala Phe Asn Asp Lys Trp Arg Ala Gln  
 290 295 300

Trp Gln Leu Ala His Arg Thr Ala Ala Gln Asp Phe Asp His Phe Tyr  
 305 310 315 320

Ala Gly Ser Glu Asn Gly Asn Leu Ile Lys Arg Asn Tyr Ala Trp Gln  
 325 330 335

Gln Thr Asp Asn Lys Thr Leu Ser Ser Asn Phe Thr Leu Asn Gly Asp  
 340 345 350

Tyr Thr Ile Gly Arg Phe Glu Asn His Leu Thr Val Gly Met Asp Tyr  
 355 360 365

Ser Arg Glu His Arg Asn Pro Thr Leu Gly Tyr Arg Gly Ser Phe Thr  
 370 375 380

Val Pro Ile Asn Pro Tyr Asp Arg Ala Ser Trp Pro Ala Ser Gly Arg  
 385 390 395 400

Leu Gln Pro Ile Leu Thr Gln Asn Arg His Lys Ala Asp Ser Tyr Gly  
 405 410 415

Ile Phe Val Gln Asn Ile Phe Ser Ala Thr Pro Asp Leu Lys Phe Val  
 420 425 430

Leu Gly Gly Arg Tyr Asp Lys Tyr Thr Phe Asn Ser Glu Asn Lys Leu  
 435 440 445

Thr Gly Asn Ser Arg Gln Tyr Ser Gly His Ser Phe Ser Pro Asn Ile  
 450 455 460

Gly Ala Val Trp Asn Ile Asn Pro Val His Thr Leu Tyr Ala Ser Tyr  
 465 470 475 480

Asn Lys Gly Phe Ala Pro Tyr Gly Gly Arg Gly Gly Tyr Leu Ser Ile  
 485 490 495

Asp Thr Leu Ser Ser Ala Val Phe Asn Ala Asp Pro Glu Tyr Thr Arg  
 500 505 510

Gln Tyr Glu Thr Gly Val Lys Ser Ser Trp Leu Asp Asp Arg Leu Ser  
 515 520 525

Thr Thr Leu Ser Ala Tyr Gln Ile Glu Arg Phe Asn Ile Arg Tyr Arg  
 530 535 540

Pro Asp Pro Lys Asn Asn Pro Tyr Ile Tyr Ala Val Ser Gly Lys His  
 545 550 555 560

Arg Ser Arg Gly Val Glu Leu Ser Ala Ile Gly Gln Ile Ile Pro Lys  
 565 570 575

Lys Leu Tyr Leu Arg Gly Ser Leu Gly Val Met Gln Ala Lys Val Val  
 580 585 590

Glu Asp Lys Glu Asn Pro Asp Arg Val Gly Ile His Leu Asn Asn Thr  
 600 605

Ser Asn Val Thr Gly Asn Leu Phe Phe Arg Tyr Thr Pro Thr Glu Asn  
610 615 620

Leu Tyr Gly Glu Ile Gly Val Thr Gly Thr Gly Lys Arg Tyr Gly Tyr  
625 630 635 640

Asn Ser Arg Asn Lys Glu Val Thr Thr Leu Pro Gly Phe Ala Arg Val  
645 650 655

Asp Ala Met Leu Gly Trp Asn His Lys Asn Val Asn Val Thr Phe Ala  
660 665 670

Ala Ala Asn Leu Phe Asn Gln Lys Tyr Trp Arg Ser Asp Ser Met Pro  
675 680 685

Gly Asn Pro Arg Gly Tyr Thr Ala Arg Val Asn Tyr Arg Phe  
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<210> 41

<211> 2112

<212> DNA

<213> *Neisseria meningitidis*

<400> 41

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&lt;210&gt; 42

&lt;211&gt; 702

&lt;212&gt; PRT

&lt;213&gt; Neisseria meningitidis

&lt;400&gt; 42

Met Lys Ile Ser Phe His Leu Ala Leu Leu Pro Thr Leu Ile Ile Ala

1

5

10

15

Ser Phe Pro Val Ala Ala Asp Thr Gln Asp Asn Gly Glu His Tyr

20

25

30

Thr Ala Thr Leu Pro Thr Val Ser Val Val Gly Gln Ser Asp Thr Ser

35

40

45

Val Leu Lys Gly Tyr Ile Asn Tyr Asp Glu Ala Ala Val Thr Arg Asn

50

55

60

Gly Gln Leu Ile Lys Glu Thr Pro Gln Thr Ile Asp Thr Leu Asn Ile

65

70

75

80

Gln Lys Asn Lys Asn Tyr Gly Thr Asn Asp Leu Ser Ser Ile Leu Glu

85

90

95

Gly Asn Ala Gly Ile Asp Ala Ala Tyr Asp Met Arg Gly Glu Ser Ile

100

105

110

Phe Leu Arg Gly Phe Gln Ala Asp Ala Ser Asp Ile Tyr Arg Asp Gly

115

120

125

Val Arg Glu Ser Gly Gln Val Arg Arg Ser Thr Ala Asn Ile Glu Arg

130

135

140



WO 01/04150

PCT/EP00/06943

Val Glu Ile Leu Lys Gly Pro Ser Ser Val Leu Tyr Gly Arg Thr Asn  
145 150 155 160

Gly Gly Gly Val Ile Asn Met Val Ser Lys Tyr Ala Asn Phe Lys Gln  
165 170 175

Ser Arg Asn Ile Gly Ala Val Tyr Gly Trp Ala Asn Arg Ser Leu Asn  
180 185 190

Met Asp Ile Asn Glu Val Leu Asn Lys Asn Val Ala Ile Arg Leu Thr  
195 200 205

Gly Glu Val Gly Arg Ala Asn Ser Phe Arg Ser Gly Ile Asp Ser Lys  
210 215 220

Asn Val Met Val Ser Pro Ser Ile Thr Val Lys Leu Asp Asn Gly Leu  
225 230 235 240

Lys Trp Thr Gly Gln Tyr Thr Tyr Asp Asn Val Glu Arg Thr Pro Asp  
245 250 255

Arg Ser Pro Thr Lys Ser Val Tyr Asp Arg Phe Gly Leu Pro Tyr Arg  
260 265 270

Met Gly Phe Ala His Arg Asn Asp Phe Val Lys Asp Lys Leu Gln Val  
275 280 285

Trp Arg Ser Asp Leu Glu Tyr Ala Phe Asn Asp Lys Trp Arg Ala Gln  
290 295 300

Trp Gln Leu Ala His Arg Thr Ala Ala Gln Asp Phe Asp His Phe Tyr  
305 310 315 320

Ala Gly Ser Glu Asn Gly Asn Leu Ile Lys Arg Asn Tyr Ala Trp Gln  
325 330 335

Gln Thr Asp Asn Lys Thr Leu Ser Ser Asn Phe Thr Leu Asn Gly Asp  
340 345 350

Tyr Thr Ile Gly Arg Phe Glu Asn His Leu Thr Val Gly Met Asp Tyr  
355 360 365

Ser Arg Glu His Arg Asn Pro Thr Leu Gly Tyr Asn Arg Ala Phe Ser  
370 375 380

Ala Ser Ile Asn Pro Tyr Asp Arg Ala Ser Trp Pro Ala Ser Gly Arg  
385 390 395 400

WO 01/04150

PCT/EP00/06943

Leu Gln Pro Ile Leu Thr Gln Asn Arg His Lys Ala Asp Ser Tyr Gly  
405 410 415

Ile Phe Val Gln Asn Ile Phe Ser Ala Thr Pro Asp Leu Lys Phe Val  
420 425 430

Leu Gly Gly Arg Tyr Asp Lys Tyr Thr Phe Asn Ser Glu Asn Lys Leu  
435 440 445

Thr Gly Ser Ser Arg Gln Tyr Ser Gly His Ser Phe Ser Pro Asn Ile  
450 455 460

Gly Ala Val Trp Asn Ile Asn Pro Val His Thr Leu Tyr Ala Ser Tyr  
465 470 475 480

Asn Lys Gly Phe Ala Pro Tyr Gly Gly Arg Gly Gly Tyr Leu Ser Ile  
485 490 495

Asp Thr Leu Ser Ser Ala Val Phe Asn Ala Asp Pro Glu Tyr Thr Arg  
500 505 510

Gln Tyr Glu Thr Gly Val Lys Ser Ser Trp Leu Asp Asp Arg Leu Ser  
515 520 525

Thr Thr Leu Ser Ala Tyr Gln Ile Glu Arg Phe Asn Ile Arg Tyr Arg  
530 535 540

Pro Asp Pro Lys Asn Asn Pro Tyr Ile Tyr Ala Val Ser Gly Lys His  
545 550 555 560

Arg Ser Arg Gly Val Glu Leu Ser Ala Ile Gly Gln Ile Ile Pro Lys  
565 570 575

Lys Leu Tyr Leu Arg Gly Ser Leu Gly Val Met Gln Ala Lys Val Val  
580 585 590

Glu Asp Lys Glu Asn Pro Asp Arg Val Gly Ile His Leu Asn Asn Thr  
595 600 605

Ser Asn Val Thr Gly Asn Leu Phe Phe Arg Tyr Thr Pro Thr Glu Asn  
610 615 620

Leu Tyr Gly Glu Ile Gly Val Thr Gly Thr Gly Lys Arg Tyr Gly Tyr  
625 630 635 640

Asp Ser Arg Asn Lys Glu Val Thr Thr Leu Pro Gly Phe Ala Arg Val  
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Gly Asn Pro Arg Gly Tyr Thr Ala Arg Val Asn Tyr Arg Phe  
690 695 700

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<210> 43
<211> 2109
<212> DNA
<213> Neisseria meningitidis
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400> 43									
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gttaccgcga	acggagacct	catcaaaagt	acgcgcagaa	ccatcgatac	catcacaatc	240			
cgaaaaaca	aacattacgg	tacgaaagat	ttgagtcca	tctccgaagg	gaatccggcg	300			
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aactcaagaa ataaagaagt gaccacgctt ccaggctttg cccgagtgtg tgccatgctc 1980  
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&lt;210&gt; 44

&lt;211&gt; 702

&lt;212&gt; PRT

&lt;213&gt; Neisseria meningitidis

&lt;400&gt; 44

Met Lys Ile Ser Phe His Leu Ala Leu Leu Pro Thr Leu Ile Ile Ala  
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Ser Phe Pro Val Ala Ala Ala Asp Thr Gln Asp Asn Gly Glu His Tyr  
 20 25 30

Thr Ala Thr Leu Pro Thr Val Ser Val Val Gly Gln Ser Asp Thr Ser  
 35 40 45

Val Leu Lys Gly Tyr Ile Asn Tyr Asp Glu Ala Ala Val Thr Arg Asn  
 50 55 60

Gly Gln Leu Ile Lys Glu Thr Pro Gln Thr Ile Asp Thr Leu Asn Ile  
 65 70 75 80

Gln Lys Asn Lys Asn Tyr Gly Thr Asn Asp Leu Ser Ser Ile Leu Glu  
 85 90 95

Gly Asn Ala Gly Ile Asp Ala Ala Tyr Asp Met Arg Gly Glu Ser Ile  
 100 105 110

Phe Leu Arg Gly Phe Gln Ala Asp Ala Ser Asp Ile Tyr Arg Asp Gly  
 115 120 125

Val Arg Glu Ser Gly Gln Val Arg Arg Ser Thr Ala Asn Ile Glu Arg  
 130 135 140

Val Glu Ile Leu Lys Gly Pro Ser Ser Val Leu Tyr Gly Arg Thr Asn  
 145 150 155 160

Gly Gly Gly Val Ile Asn Met Val Ser Lys Tyr Ala Asn Phe Lys Gln  
 165 170 175

Ser Arg Asn Ile Gly Ala Val Tyr Gly Ser Trp Ala Asn Arg Ser Leu  
 180 185 190

Asn Met Asp Ile Asn Glu Val Leu Asn Lys Asn Val Ala Ile Arg Leu

195	200	205
Thr Gly Glu Val Gly Arg Ala Asn Ser Phe Arg Ser Gly Ile Asp Ser		
210	215	220
Lys Asn Val Met Val Ser Pro Ser Ile Thr Val Lys Leu Asp Asn Gly		
225	230	240
Leu Lys Trp Thr Gly Gln Tyr Thr Tyr Asp Asn Val Glu Arg Thr Pro		
	245	255
Asp Arg Ser Pro Thr Lys Ser Val Tyr Asp Arg Phe Gly Leu Pro Tyr		
	260	270
Arg Met Gly Phe Ala His Arg Asn Asp Phe Val Lys Asp Lys Leu Gln		
275	280	285
Val Trp Arg Ser Asp Leu Glu Tyr Ala Phe Asn Asp Lys Trp Arg Ala		
290	295	300
Gln Trp Gln Leu Ala His Arg Thr Ala Ala Gln Asp Phe Asp His Phe		
305	310	320
Tyr Ala Gly Ser Glu Asn Gly Asn Leu Ile Lys Arg Asp Tyr Ala Trp		
	325	335
Gln Gln Thr Asp Asn Lys Thr Leu Ser Ser Asn Leu Thr Leu Asn Gly		
	340	350
Asp Tyr Thr Ile Gly Arg Phe Glu Asn His Leu Thr Val Gly Met Asp		
355	360	365
Tyr Ser Arg Glu His Arg Asn Pro Thr Leu Gly Tyr Arg Gly Ser Phe		
370	375	380
Thr Val Pro Ile Asn Pro Tyr Asp Arg Ala Ser Trp Pro Ala Ser Gly		
385	390	400
Arg Leu Gln Pro Ile Leu Thr Gln Asn Arg His Lys Ala Asp Ser Tyr		
	405	415
Gly Ile Phe Val Gln Asn Ile Phe Ser Ala Thr Pro Asp Leu Lys Phe		
	420	430
Val Leu Gly Gly Arg Tyr Asp Lys Tyr Thr Phe Asn Ser Glu Asn Lys		
435	440	445
Leu Thr Gly Asn Ser Arg Gln Tyr Ser Gly His Ser Phe Ser Pro Asn		

450	455	460
Ile Gly Ala Val Trp Asn	Ile Asn Pro Val His Thr Leu Tyr Ala Ser	
465	470	475 480
Tyr Asn Lys Gly Phe Ala Pro Tyr Gly Gly Arg Gly Tyr Leu Ser Ile		
	485	490 495
Asp Thr Ser Ser Ala Ala Val Phe Asn Ala Ala Pro Glu Tyr Thr Arg		
	500	505 510
Gln Tyr Glu Thr Gly Val Lys Ser Ser Trp Leu Asp Asp Arg Leu Ser		
	515	520 525
Thr Thr Leu Ser Ala Tyr Gln Ile Glu Arg Phe Asn Ile Arg Tyr Arg		
	530	535 540
Pro Asp Pro Lys Asn Asn Pro Tyr Ile Tyr Ala Val Ser Gly Lys His		
	545	550 555 560
Arg Ser Arg Gly Val Glu Leu Ser Ala Ile Gly Gln Ile Ile Pro Lys		
	565	570 575
Lys Leu Tyr Leu Arg Gly Ser Leu Gly Val Met Gln Ala Lys Val Val		
	580	585 590
Glu Asp Lys Glu Asn Pro Asp Arg Val Gly Ile His Leu Asn Asn Thr		
	595	600 605
Ser Asn Val Thr Gly Asn Leu Phe Phe Arg Tyr Thr Pro Thr Glu Asn		
	610	615 620
Leu Tyr Gly Glu Ile Gly Val Thr Gly Thr Gly Lys Arg Tyr Gly Tyr		
	625	630 635 640
Asn Ser Arg Asn Lys Glu Val Thr Thr Leu Pro Gly Phe Ala Arg Val		
	645	650 655
Asp Ala Met Leu Gly Trp Asn His Lys Asn Val Asn Val Thr Phe Ala		
	660	665 670
Ala Ala Asn Leu Leu Asn Gln Lys Tyr Trp Arg Ser Asp Ser Met Pro		
	675	680 685
Gly Asn Pro Arg Gly Tyr Thr Ala Arg Val Asn Tyr Arg Phe		
	690	695 700

&lt;210&gt; 45

&lt;211&gt; 2108

&lt;212&gt; DNA

<213> *Neisseria meningitidis*

&lt;400&gt; 45

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&lt;210&gt; 46

&lt;211&gt; 697

&lt;212&gt; PRT

<213> *Neisseria meningitidis*

&lt;400&gt; 46

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Met Lys Ile Ser Phe His Leu Ala Leu Leu Pro Thr Leu Ile Ile Ala
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Ser Phe Pro Val Ala Ala Ala Asp Thr Gln Asp Asn Gly Glu His Tyr
          20             25             30

Thr Ala Thr Leu Pro Thr Val Ser Val Val Gly Gln Ser Asp Thr Ser
          35             40             45

Val Leu Lys Gly Tyr Ile Asn Tyr Asp Glu Ala Ala Val Thr Arg Asn
          50             55             60

Gly Gln Leu Ile Lys Glu Thr Pro Gln Thr Ile Asp Thr Leu Asn Ile
 65             70             75             80

Gln Lys Asn Lys Asn Tyr Gly Thr Asn Asp Leu Ser Ser Ile Leu Glu
          85             90             95

Gly Asn Ala Gly Ile Asp Ala Ala Tyr Asp Met Arg Gly Glu Ser Ile
        100             105             110

Phe Leu Arg Gly Phe Gln Ala Asp Ala Ser Asp Ile Tyr Arg Asp Gly
        115             120             125

Val Arg Glu Ser Gly Gln Val Arg Arg Ser Thr Ala Asn Ile Glu Arg
        130             135             140

Val Glu Ile Leu Lys Gly Pro Ser Ser Val Leu Tyr Gly Arg Thr Asn
        145             150             155             160

Gly Gly Gly Val Ile Asn Met Val Ser Lys Tyr Ala Asn Phe Lys Gln
        165             170             175

Ser Arg Asn Ile Gly Ala Val Tyr Gly Ser Trp Ala Asn Arg Ser Leu
        180             185             190

Asn Met Asp Ile Asn Glu Val Leu Asn Lys Asn Val Ala Ile Arg Leu
        195             200             205

Thr Gly Glu Val Gly Arg Ala Asn Ser Phe Arg Ser Gly Ile Asp Ser
        210             215             220

Lys Asn Val Met Val Ser Pro Ser Ile Thr Val Lys Leu Asp Asn Gly
        225             230             235             240

Leu Lys Trp Thr Gly Gln Tyr Thr Tyr Asp Asn Val Glu Arg Thr Pro
        245             250             255

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Asp Arg Ser Pro Thr Lys Ser Val Tyr Asp Arg Phe Gly Leu Pro Tyr  
 260 265 270

Arg Met Gly Phe Ala His Pro Asn Asp Phe Val Lys Asp Lys Leu Gln  
 275 280 285

Val Trp Arg Ser Asp Leu Glu Tyr Ala Phe Asn Asp Lys Trp Arg Ala  
 290 295 300

Gln Trp Gln Leu Ala His Arg Thr Ala Ala Gln Asp Phe Asp His Phe  
 305 310 315 320

Tyr Ala Gly Ser Glu Asn Gly Ser Arg Ile Lys Arg Asn Tyr Ala Trp  
 325 330 335

Gln Gln Thr Asp Asn Lys Thr Leu Ser Ser Asn Phe Thr Leu Asn Gly  
 340 345 350

Asp Tyr Thr Ile Gly Arg Phe Glu Asn His Leu Thr Val Gly Met Asp  
 355 360 365

Tyr Ser Arg Glu His Arg Asn Pro Thr Leu Gly Tyr Arg Gly Ser Phe  
 370 375 380

Thr Val Pro Ile Asn Pro Tyr Asp Arg Ala Ser Trp Pro Ala Ser Gly  
 385 390 395 400

Arg Leu Gln Pro Ile Leu Thr Gln Asn Arg His Lys Ala Asp Ser Tyr  
 405 410 415

Gly Ile Phe Val Gln Asn Ile Phe Ser Ala Thr Pro Asp Leu Lys Phe  
 420 425 430

Val Leu Gly Gly Arg Tyr Asp Lys Tyr Thr Phe Asn Ser Glu Asn Lys  
 435 440 445

Leu Thr Gly Asn Ser Arg Gln Tyr Ser Gly His Ser Phe Ser Pro Asn  
 450 455 460

Ile Gly Ala Val Trp Asn Ile Asn Pro Val His Thr Leu Tyr Ala Ser  
 465 470 475 480

Tyr Asn Lys Gly Phe Ala Pro Tyr Gly Gly Arg Gly Tyr Leu Ser Ile  
 485 490 495

Asp Thr Ser Ser Ala Ala Val Phe Asn Ala Ala Pro Glu Tyr Thr Pro  
 500 505 510

Asn Thr Lys Pro Ala Ser Lys Ala Val Gly Trp Thr Ile Val Trp Thr  
 515 520  
 Pro Pro Cys Arg Phe Thr Lys Ser Asn Ala Ser Ile Ser Ala Thr Ala  
 530 535 540  
 Pro Ile Gln Lys Thr Thr Leu Ile Phe Met Arg Leu Ala Ala Asn Thr  
 545 550 555 560  
 Val Arg Ala Ala Trp Asn Cys Pro Pro Ser Gly Lys Ser Ser Pro Lys  
 565 570 575  
 Asn Ser Ile Cys Ala Val Arg Trp Ala Cys Arg Arg Lys Ser Leu Lys  
 580 585 590  
 Thr Lys Lys Ile Pro Thr Glu Trp Ala Ser Ile Ile Thr Pro Ala Thr  
 595 600 605  
 Leu Pro Ala Thr Cys Phe Ser Val Ile Pro Arg Pro Lys Thr Ser Thr  
 610 615 620  
 Ala Lys Ser Ala Pro Val Arg Ala Asn Ala Thr Val Thr Thr Gln Glu  
 625 630 635 640  
 Ile Lys Lys Leu Arg Phe Gln Ala Leu Pro Glu Leu Met Pro Cys Leu  
 645 650 655  
 Ala Gly Thr Ile Lys Met Leu Thr Leu Pro Leu Pro Gln Pro Ile Cys  
 660 665 670  
 Ser Ile Lys Asn Ile Gly Val Arg Thr Leu Cys Arg Val Ile Arg Ala  
 675 680 685  
 Ala Ile Leu Pro Gly Ile Thr Val Ser  
 690 695

&lt;210&gt; 47

&lt;211&gt; 2113

&lt;212&gt; DNA

&lt;213&gt; Neisseria meningitidis

&lt;400&gt; 47

atgcaaatatc catttcattt ggctttatta ccacgctga ttattgcttc cttccctgtt 60  
 gtcgccgcg atacgcagga caatggtgaa cattacaccg ccacgctacc tacggtttcc 120  
 gtgtctggac agtccgacac cagcgctactc aaaggctaca tcaactacga cgaagccgcc 180  
 gttaccgcga acggacagct catcaagaa acgccgcgcaaa ccatcgatac gctcaatatc 240

cagaaaaaca aaaattacgg cacgaacgat ttgagttcca tctcgaagg caatgccggc 300  
 atcgacgcgg cctacgatat gcgcggcgaa agcattttcc tgcgcggctt tcaagccgac 360  
 gcattctgata ttaccgcgga cggcgtagcg gaaagcgggc aggtgcgcgc tagcaccgcc 420  
 aacatcgagc gcgtggaagt cctgaaaggt ccgtcctccg tgctttatgg gcgtaccaac 480  
 ggccggcggtg tcatcaacat ggtcagcaaa tacgccaact tcaaacaaag ccgtaatatc 540  
 ggtacgggtt atggttcgtg ggcaaacgt agcctgaata tggacatcaa cgaagtgcgt 600  
 aacaaaaacg tcgcatcggt tctcaccggc gaagtcgggc gcgccaattc gtcccgagc 660  
 ggcatagaca gaaaaatgt catggtttcg ccacgacatta ccgtcaaaact cgacaacggc 720  
 ttgaagtggg cggggcaata cacctacgac aatgtggagc gcacgcgcga ccgcagtcgc 780  
 accaagtcgc tgtacgaccg ctccggactg ccttaccgca tgggggttcgc ccaccggaac 840  
 gattttgcga aagacaagct gcaagtttgg cgttcggacc ttgaatacgc cttcaacgac 900  
 aaatggcggt cccaatggca gctcggccac cgcacggcgg cgcaggattt tgatcatttc 960  
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 aacaaaaccc tgcgttccaa cttaacgcctc aacggcgact acaccatcgg ccgttttgaa 1080  
 aaccacctga ccgtaggcat ggattacagc cgcgaacacc gcaaccgcac attgggtttc 1140  
 agcagcgccct ttccgcctc catcaacccc tacgaccgcg caagctgggc ggcttcgggc 1200  
 agattgcagc ctattctgac ccaaaacccg cacaagccg actcctacgg catctttgtg 1260  
 aaaaacatct tctccgcac gcccgatttg aaattcgctc tcggcgggccg ttacgacaaa 1320  
 tacaccttta attccgaaaa caaactcacc ggacgacgcc gccaatagc ggacactgc 1380  
 ttcagcccca acatcgggcg agtgtggaac atcaatcccg tccacacact ttacgcctcg 1440  
 tataacaaag gcttcgcgcc ttatggcgga cgcggcggtt atttgagcat cgatacgttg 1500  
 tcttcgcgct tgttcaacgc cgaccccgag tacaccgcgc aatacgaaac cggcgtgaaa 1560  
 agcagttggc tggacgaccg cctcagcact acgttgtctg cctaccaaat cgaacgcttc 1620  
 aatatccgct accgcccga tccaaaaaac aacccttata tttatgcgtt tagcgcgaaa 1680  
 caccgttcgc gcggcggtga attgtccgcc atcgggcaaa tcatcccaa aaaaactcta 1740  
 tctgcgcggt tcgttggttg tgatgcagcg gaaagtcgtt gaagacaaag aaaatcccga 1800  
 ccgagttggc atccatttga ataaccacag caacgttacc ggcaacctgt tttccgttga 1860  
 taccgccgac gaaaacctct acggcgaaat cggcgtaacc ggtacaggca aacgctacgg 1920  
 ttacgactca agaaataaag aagtgaactac gcttcacggc tttcccgag ttgatgccat 1980  
 gcttggtctg aaccataaaa atgttaacgt tacctttgcc gcagccaatc tgttcaatca 2040  
 aaaaatttgg cgttcggact ctatgccggg taatccgcgc ggtatactg cccgggtaaa 2100  
 ttaccgttcc tga 2113

&lt;210&gt; 48

&lt;211&gt; 697

&lt;212&gt; PRT

<213> *Neisseria meningitidis*

&lt;400&gt; 48

Met Gln Ile Pro Phe His Leu Ala Leu Leu Pro Thr Leu Ile Ile Ala

1

5

10

15

Ser Phe Pro Val Ala Ala Ala Asp Thr Gln Asp Asn Gly Glu His Tyr

20

25

30

Thr Ala Thr Leu Pro Thr Val Ser Val Val Gly Gln Ser Asp Thr Ser

35

40

45

Val Leu Lys Gly Tyr Ile Asn Tyr Asp Glu Ala Ala Val Thr Arg Asn  
50 55 60

Gly Gln Leu Ile Lys Glu Thr Pro Gln Thr Ile Asp Thr Leu Asn Ile  
65 70 75 80

Gln Lys Asn Lys Asn Tyr Gly Thr Asn Asp Leu Ser Ser Ile Leu Glu  
85 90 95

Gly Asn Ala Gly Ile Asp Ala Ala Tyr Asp Met Arg Gly Glu Ser Ile  
100 105 110

Phe Leu Arg Gly Phe Gln Ala Asp Ala Ser Asp Ile Tyr Arg Asp Gly  
115 120 125

Val Arg Glu Ser Gly Gln Val Arg Arg Ser Thr Ala Asn Ile Glu Arg  
130 135 140

Val Glu Ile Leu Lys Gly Pro Ser Ser Val Leu Tyr Gly Arg Thr Asn  
145 150 155 160

Gly Gly Gly Val Ile Asn Met Val Ser Lys Tyr Ala Asn Phe Lys Gln  
165 170 175

Ser Arg Asn Ile Gly Thr Val Tyr Gly Ser Trp Ala Asn Arg Ser Leu  
180 185 190

Asn Met Asp Ile Asn Glu Val Leu Asn Lys Asn Val Ala Ile Arg Leu  
195 200 205

Thr Gly Glu Val Gly Arg Ala Asn Ser Phe Arg Ser Gly Ile Asp Ser  
210 215 220

Lys Asn Val Met Val Ser Pro Ser Ile Thr Val Lys Leu Asp Asn Gly  
225 230 235 240

Leu Lys Trp Thr Gly Gln Tyr Thr Tyr Asp Asn Val Glu Arg Thr Pro  
245 250 255

Asp Arg Ser Pro Thr Lys Ser Val Tyr Asp Arg Phe Gly Leu Pro Tyr  
260 265 270

Arg Met Gly Phe Ala His Arg Asn Asp Phe Val Lys Asp Lys Leu Gln  
275 280 285

Val Trp Arg Ser Asp Leu Glu Tyr Ala Phe Asn Asp Lys Trp Arg Ala  
290 295 300

Gln Trp Gln Leu Ala His Arg Thr Ala Ala Gln Asp Phe Asp His Phe  
305 310 315 320

Tyr Ala Gly Ser Glu Asn Gly Asn Leu Ile Lys Arg Asn Tyr Ala Trp  
325 330 335

Gln Gln Thr Asp Asn Lys Thr Leu Ser Ser Asn Leu Thr Leu Asn Gly  
340 345 350

Asp Tyr Thr Ile Gly Arg Phe Glu Asn His Leu Thr Val Gly Met Asp  
355 360 365

Tyr Ser Arg Glu His Arg Asn Pro Thr Leu Gly Phe Ser Ser Ala Phe  
370 375 380

Ser Ala Ser Ile Asn Pro Tyr Asp Arg Ala Ser Trp Pro Ala Ser Gly  
385 390 395 400

Arg Leu Gln Pro Ile Leu Thr Gln Asn Arg His Lys Ala Asp Ser Tyr  
405 410 415

Gly Ile Phe Val Gln Asn Ile Phe Ser Ala Thr Pro Asp Leu Lys Phe  
420 425 430

Val Leu Gly Gly Arg Tyr Asp Lys Tyr Thr Phe Asn Ser Glu Asn Lys  
435 440 445

Leu Thr Gly Ser Ser Arg Gln Tyr Ser Gly His Ser Phe Ser Pro Asn  
450 455 460

Ile Gly Ala Val Trp Asn Ile Asn Pro Val His Thr Leu Tyr Ala Ser  
465 470 475 480

Tyr Asn Lys Gly Phe Ala Pro Tyr Gly Gly Arg Gly Gly Tyr Leu Ser  
485 490 495

Ile Asp Thr Leu Ser Ser Ala Val Phe Asn Ala Asp Pro Glu Tyr Thr  
500 505 510

Arg Gln Tyr Glu Thr Gly Val Lys Ser Ser Trp Leu Asp Asp Arg Leu  
515 520 525

Ser Thr Thr Leu Ser Ala Tyr Gln Ile Glu Arg Phe Asn Ile Arg Tyr  
530 535 540

Arg Pro Asp Pro Lys Asn Asn Pro Tyr Ile Tyr Ala Val Ser Gly Lys  
545 550 555 560

His Arg Ser Arg Gly Val Glu Leu Ser Ala Ile Gly Gln Ile Ile Pro  
 565 570 575  
 Lys Lys Thr Leu Ser Ala Arg Phe Val Gly Arg Asp Ala Gly Glu Ser  
 580 585 590  
 Arg Arg Gln Arg Lys Ser Arg Pro Ser Gly His Pro Phe Glu His Gln  
 595 600 605  
 Gln Arg Tyr Arg Gln Pro Val Phe Pro Leu Tyr Pro Asp Arg Lys Pro  
 610 615 620  
 Leu Arg Arg Asn Arg Arg Asn Arg Tyr Arg Gln Thr Leu Arg Leu Arg  
 625 630 635 640  
 Leu Lys Lys Arg Ser Asp Tyr Ala Ser Arg Leu Cys Pro Ser Cys His  
 645 650 655  
 Ala Trp Leu Glu Pro Lys Cys Arg Tyr Leu Cys Arg Ser Gln Ser Val  
 660 665 670  
 Gln Ser Lys Ile Leu Ala Phe Gly Leu Tyr Ala Gly Ser Ala Arg Leu  
 675 680 685  
 Tyr Cys Pro Gly Lys Leu Pro Phe Leu  
 690 695

&lt;210&gt; 49

&lt;211&gt; 2112

&lt;212&gt; DNA

&lt;213&gt; Neisseria meningitidis

&lt;400&gt; 49

atgaaaatat catttcattt agctttatta cccacgctga ttattgcttc cttccctgtt 60  
 gctgcgcgcg atacgcagga caatggtgaa cattacacgc ccactctgcc caccgtttcc 120  
 gtggtcggac agtcgcagac cagcgtactc aaaggctaca tcaactacga cgaagccgcg 180  
 gttaccgcga acggacagct catcaagaa acgccgcaaa ccacgcatac gtcgaatatc 240  
 cagaaaaaca aaaattacgcg tacgaacgat ttgagtcca tctcgaagg caatgccggc 300  
 atcgacgcgt cctacgatat gcgcgcgcgaa agcattttcc tgcgcggttt tcaagccgac 360  
 gcatccgata ttaccgcga cgcgctgcgc gaaagcggac aagtgcgcgc cagtactgcc 420  
 aacatcgagc gcgtggaaat cctgaaaggc ccgtcttcgc tgctttacgc ccgcaccaac 480  
 ggcgcgcgcg tcatcaacat ggtcagcaaa tacgccaaact tcaaacaaag ccgcacaatc 540  
 ggtgcgcgttt acggttcgtg ggcaaacgcg agcctgaata tggacattaa cgaagtgttg 600  
 aacaaaaacg tcgccatccg tctaccgcgc gaagtcgggc gcgccaatc gttccgcagc 660  
 ggcatagaca gcaaaaatgt catggtttcg ccagcatta ccgtcaaat cgacaacgcg 720  
 ttgaagtgga cggggcaata cacctacgac aatgtggagc gcacgcccga ccgcagtcgc 780  
 accaagtccg tgtacgacgc cttcggactg ccttaccgca tgggggttcg ccaccggaac 840

gattttgtca aagacaagct gcaagtttgg cgctccgacc ttgaatacgc cttcaacgac 900  
 aaatggcggt cccaatggca gctcgccac cgacgaggcg cgcaggattt tgatcatttc 960  
 tatgcaggga gcgaaaatgg caacttaatc aaacgttaact acgcctggca gcagaccgac 1020  
 aacaaaaacc ttgtcgtcaa ttccacgcta aacggcgact acaccatcgg ccgttttgaa 1080  
 aaccacttga ccgtaggcat ggattacagc cggaacacc gcaacccgac cttagggtac 1140  
 agccgcgcct ttactgcttc catcgatcca tacgaccgag caagctggcc ggcttcgggc 1200  
 agattgcagc ctatctctac ccaaaaccgc cacaagcgc actcctacgg catctttgtg 1260  
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 tacaccttta attccgaaaa caaactcacc ggcagcagcc gccaatagcg cggacactcg 1380  
 ttcagcccca acatcgggcg agtggtggaac atcaatcccg tccacacact ttacgcctcg 1440  
 tataataaag gcttcgcgccc ttatggcgga cgccggcggt atttgagcat caacacgtcg 1500  
 tcttccgcgg tggtcaacgc cgaccccgag tacacccgcc aatacgaac cggttgaaa 1560  
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 aatatccgct accgcccga cgagcaaaat gatccctaca cttgggcagt cggcgccaaa 1680  
 caccgttcgc ggcgcgtgga attgtccgcc atcgggcaaa tcactcccaa aaaactctat 1740  
 ctgcgcggtt cgttggcggt gatgcaggcg aaagtctgtg aagacaaaaga aaatcccgac 1800  
 cgagtgggga tccatttgaa taacaccagc aacgttaccg gcaacctgtt ttccggttat 1860  
 accccgaccg aaaaacctta cggcgaaatc ggcgtaaccg gtacaggcaa acgctacggt 1920  
 taccactcaa gaaataaaga agtgactacg ctccaggcgt ttgcccgagt tgatgccatg 1980  
 cttggctgga accataaaaa tgtaacatt acccttgcgc cagccaatct gctcaatcaa 2040  
 aaatattggc gttcggatgc catgcccggc ggcgcgcgca cttatacggc gcgggttaat 2100  
 tacagtttct aa 2112

&lt;210&gt; 50

&lt;211&gt; 703

&lt;212&gt; PRT

<213> *Neisseria meningitidis*

&lt;400&gt; 50

Met Lys Ile Ser Phe His Leu Ala Leu Leu Pro Thr Leu Ile Ile Ala  
 1 5 10 15

Ser Phe Pro Val Ala Ala Ala Asp Thr Gln Asp Asn Gly Glu His Tyr  
 20 25 30

Thr Ala Thr Leu Pro Thr Val Ser Val Val Gly Gln Ser Asp Thr Ser  
 35 40 45

Val Leu Lys Gly Tyr Ile Asn Tyr Asp Glu Ala Ala Val Thr Arg Asn  
 50 55 60

Gly Gln Leu Ile Lys Glu Thr Pro Gln Thr Ile Asp Thr Leu Asn Ile  
 65 70 75 80

Gln Lys Asn Lys Asn Tyr Gly Thr Asn Asp Leu Ser Ser Ile Leu Glu  
 85 90 95

Gly Asn Ala Gly Ile Asp Ala Ala Tyr Asp Met Arg Gly Glu Ser Ile

WO 01/04150

PCT/EP00/06943

100	105	110
Phe Leu Arg Gly Phe Gln Ala Asp Ala Ser Asp Ile Tyr Arg Asp Gly		
115	120	125
Val Arg Glu Ser Gly Gln Val Arg Arg Ser Thr Ala Asn Ile Glu Arg		
130	135	140
Val Glu Ile Leu Lys Gly Pro Ser Ser Val Leu Tyr Gly Arg Thr Asn		
145	150	155
Gly Gly Gly Val Ile Asn Met Val Ser Lys Tyr Ala Asn Phe Lys Gln		
165	170	175
Ser Arg Asn Ile Gly Ala Val Tyr Gly Ser Trp Ala Asn Arg Ser Leu		
180	185	190
Asn Met Asp Ile Asn Glu Val Leu Asn Lys Asn Val Ala Ile Arg Leu		
195	200	205
Thr Gly Glu Val Gly Arg Ala Asn Ser Phe Arg Ser Gly Ile Asp Ser		
210	215	220
Lys Asn Val Met Val Ser Pro Ser Ile Thr Val Lys Leu Asp Asn Gly		
225	230	235
Leu Lys Trp Thr Gly Gln Tyr Thr Tyr Asp Asn Val Glu Arg Thr Pro		
245	250	255
Asp Arg Ser Pro Thr Lys Ser Val Tyr Asp Arg Phe Gly Leu Pro Tyr		
260	265	270
Arg Met Gly Phe Ala His Arg Asn Asp Phe Val Lys Asp Lys Leu Gln		
275	280	285
Val Trp Arg Ser Asp Leu Glu Tyr Ala Phe Asn Asp Lys Trp Arg Ala		
290	295	300
Gln Trp Gln Leu Ala His Arg Thr Ala Ala Gln Asp Phe Asp His Phe		
305	310	315
Tyr Ala Gly Ser Glu Asn Gly Asn Leu Ile Lys Arg Asn Tyr Ala Trp		
325	330	335
Gln Gln Thr Asp Asn Lys Thr Leu Ser Ser Asn Phe Thr Leu Asn Gly		
340	345	350
Asp Tyr Thr Ile Gly Arg Phe Glu Asn His Leu Thr Val Gly Met Asp		



355	360	365
Tyr Ser Arg Glu His Arg Asn Pro Thr Leu Gly Tyr Ser Arg Ala Phe 370 375 380		
Thr Ala Ser Ile Asp Pro Tyr Asp Arg Ala Ser Trp Pro Ala Ser Gly 385 390 395 400		
Arg Leu Gln Pro Ile Leu Thr Gln Asn Arg His Lys Ala Asp Ser Tyr 405 410 415		
Gly Ile Phe Val Gln Asn Ile Phe Ser Ala Thr Pro Asp Leu Lys Phe 420 425 430		
Val Leu Gly Gly Arg Tyr Asp Lys Tyr Thr Phe Asn Ser Glu Asn Lys 435 440 445		
Leu Thr Gly Ser Ser Arg Gln Tyr Ser Gly His Ser Phe Ser Pro Asn 450 455 460		
Ile Gly Ala Val Trp Asn Ile Asn Pro Val His Thr Leu Tyr Ala Ser 465 470 475 480		
Tyr Asn Lys Gly Phe Ala Pro Tyr Gly Gly Arg Gly Gly Tyr Leu Ser 485 490 495		
Ile Asn Thr Ser Ser Ser Ala Val Phe Asn Ala Asp Pro Glu Tyr Thr 500 505 510		
Arg Gln Tyr Glu Thr Gly Val Lys Ser Ser Trp Leu Asp Asp Arg Leu 515 520 525		
Ser Thr Thr Leu Ser Ala Tyr Gln Ile Glu Arg Phe Asn Ile Arg Tyr 530 535 540		
Arg Pro Asp Glu Gln Asn Asp Pro Tyr Thr Trp Ala Val Gly Gly Lys 545 550 555 560		
His Arg Ser Arg Gly Val Glu Leu Ser Ala Ile Gly Gln Ile Ile Pro 565 570 575		
Lys Lys Leu Tyr Leu Arg Gly Ser Leu Gly Val Met Gln Ala Lys Val 580 585 590		
Val Glu Asp Lys Glu Asn Pro Asp Arg Val Gly Ile His Leu Asn Asn 595 600 605		
Thr Ser Asn Val Thr Gly Asn Leu Phe Phe Arg Tyr Thr Pro Thr Glu		

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PCT/EP00/06943

610

615

620

Asn Leu Tyr Gly Glu Ile Gly Val Thr Gly Thr Gly Lys Arg Tyr Gly  
625 630 635 640

Tyr Asn Ser Arg Asn Lys Glu Val Thr Thr Leu Pro Gly Phe Ala Arg  
645 650 655

Val Asp Ala Met Leu Gly Trp Asn His Lys Asn Val Asn Ile Thr Phe  
660 665 670

Ala Ala Ala Asn Leu Leu Asn Gln Lys Tyr Trp Arg Ser Asp Ala Met  
675 680 685

Pro Gly Ala Pro Arg Thr Tyr Thr Ala Arg Val Asn Tyr Ser Phe  
690 695 700

<210> 51

<211> 2112

<212> DNA

<213> Neisseria meningitidis

<400> 51

atgaaaaatat catttccattt agctttatta cccacgctga ttattgtcttc cttccctgtt 60  
gctgcgcgcg atacgcagga caatggtgaa cattacaccg ccactctgcc caccgtttcc 120  
gtggtcggac agtccgacac cagcgctactc aaaggctaca tcaactacga cgaagccgcc 180  
gttaccgcga acggacagct catcaaaaga acgcccga aaatcgatgc gctcaatc 240  
cagaaaaaca aaaattacgg tacgaacgat ttgagttcca tcttcgaagg caatgccggc 300  
atcgacgctg cctacgatat gcgcggtgaa agcattttcc tgcgcggttt tcaagccgac 360  
gcacccgata ttaccgcga cggcgctgcc gaaagcggac aagtgcgcgc cagtactgcc 420  
aacatcgagc gcgtgggaaat cctgaaaggc ccgtcttcgc tgctttacgg ccgcaccaac 480  
ggcggcgggc tcatcaacat ggtcagcaaa tacgccaact tcaaaaaag ccgcaacatc 540  
ggagcgggtt acggctcatg ggcaaaacgc agcctgaata tggacattaa cgaagtgtg 600  
aacaaaaacg tcgccatcgc tctcaccggc gaagtcgggc gcgccaattc gttccgcagc 660  
ggcatagaca gcaaaaaatg catggtttcg cccagcatta ccgtcaaaat cgacaacggc 720  
ttgaagtgga cggggcaata cactacgac aatgtggagc gcacgcccga ccgcagtcgc 780  
accaagtcgc tgtacgacgc cttcggactg ccttaccgca tggggttcgc ccaccggaac 840  
gattttgtca aagacaagct gcaagtttgc cgttccgacc ttgaatacgc cttcaacgac 900  
aaatggcgct cccaatggca gctcgcgcc cgcacggcgc cgcaggattt tgatcatttc 960  
tatgcaggca gcgaaaaatg caacttaact aaacgtaact acgcttgcca gcagaccgac 1020  
aacaaaaacc tgctgtccaa cttaacgctc aacggcgact acaccatcgc ccgttttgaa 1080  
aaccacctga ccgtaggcat ggtattacgc cgcgaacacc gcaaccgcac attgggtttc 1140  
agcagcgcc tttccgcctc catcaacccc tacgaccggc caagctggcc ggcttcgggc 1200  
agattgcagc ctattctgac ccaaaacgcg cacaaagccg actcctacgc catctttgtg 1260  
caaaacatct tctccgcaac gcccgatttg aaattcgtcc tcggcgccgc ttacgacaaa 1320  
tacaccttta attccgaaaa caaactcacc ggcagcagcc gcccaatacag cggacactcg 1380  
ttcagcccca acatcggcgc agtgtggaac atcaatcccg tccacacact ttacgcctcg 1440

tataacaaag gcttcgcgcc ttatggcgga cgcggcggct atttgagcat cgatacgttg 1500  
 tcttcgcgcg tggtcaacgc cgaccccgag tacaccgcgc aatacgaac cggcgtgaaa 1560  
 agcagttggc tggacgaccg cctcagcact acgttgctct cctaccaaat cgaacgcttc 1620  
 aatatccgct accgccccga tccaaaaaac aacccttata tttatcggtg tagcggcaaa 1680  
 caccgttcgc gcggcggtga attgtccgcc atcggggcaa tcattcccaa aaaactctat 1740  
 ctgcgcggtt cgttgggcgt gatgcaggcg aaagtcggtg aagacaaaga aaatcccgac 1800  
 cgagtgggca tccatttgaa taataaccagc aacgttacgc gcaacctgtt ttccggttat 1860  
 accccgaccg aaaacctcta cggcgaaatc ggcgtaaccg gtacaggcaa acgctacggt 1920  
 tacaactcaa gaaataaaga agtgactacg ctccaggct ttgcccgagt tgatgccatg 1980  
 cttggctgga accataaaaa tgttaacgtt acctttgccg cagccaatct gctcaatcaa 2040  
 aaatattggc gttcggactc tatgccgggt aatccgcgcg gctatactgc cggggtaaat 2100  
 taccggttct ga 2112

&lt;210&gt; 52

&lt;211&gt; 703

&lt;212&gt; PRT

&lt;213&gt; Neisseria meningitidis

&lt;400&gt; 52

Met Lys Ile Ser Phe His Leu Ala Leu Leu Pro Thr Leu Ile Ile Ala  
 1 5 10 15

Ser Phe Pro Val Ala Ala Ala Asp Thr Gln Asp Asn Gly Glu His Tyr  
 20 25 30

Thr Ala Thr Leu Pro Thr Val Ser Val Val Gly Gln Ser Asp Thr Ser  
 35 40 45

Val Leu Lys Gly Tyr Ile Asn Tyr Asp Glu Ala Ala Val Thr Arg Asn  
 50 55 60

Gly Gln Leu Ile Lys Glu Thr Pro Gln Thr Ile Asp Thr Leu Asn Ile  
 65 70 75 80

Gln Lys Asn Lys Asn Tyr Gly Thr Asn Asp Leu Ser Ser Ile Leu Glu  
 85 90 95

Gly Asn Ala Gly Ile Asp Ala Ala Tyr Asp Met Arg Gly Glu Ser Ile  
 100 105 110

Phe Leu Arg Gly Phe Gln Ala Asp Ala Ser Asp Ile Tyr Arg Asp Gly  
 115 120 125

Val Arg Glu Ser Gly Gln Val Arg Arg Ser Thr Ala Asn Ile Glu Arg  
 130 135 140

Val Glu Ile Leu Lys Gly Pro Ser Ser Val Leu Tyr Gly Arg Thr Asn  
 145 150 155 160

Gly Gly Gly Val Ile Asn Met Val Ser Lys Tyr Ala Asn Phe Lys Gln  
 165 170 175

Ser Arg Asn Ile Gly Ala Val Tyr Gly Ser Trp Ala Asn Arg Ser Leu  
 180 185 190

Asn Met Asp Ile Asn Glu Val Leu Asn Lys Asn Val Ala Ile Arg Leu  
 195 200 205

Thr Gly Glu Val Gly Arg Ala Asn Ser Phe Arg Ser Gly Ile Asp Ser  
 210 215 220

Lys Asn Val Met Val Ser Pro Ser Ile Thr Val Lys Leu Asp Asn Gly  
 225 230 235 240

Leu Lys Trp Thr Gly Gln Tyr Thr Tyr Asp Asn Val Glu Arg Thr Pro  
 245 250 255

Asp Arg Ser Pro Thr Lys Ser Val Tyr Asp Arg Phe Gly Leu Pro Tyr  
 260 265 270

Arg Met Gly Phe Ala His Arg Asn Asp Phe Val Lys Asp Lys Leu Gln  
 275 280 285

Val Trp Arg Ser Asp Leu Glu Tyr Ala Phe Asn Asp Lys Trp Arg Ala  
 290 295 300

Gln Trp Gln Leu Ala His Arg Thr Ala Ala Gln Asp Phe Asp His Phe  
 305 310 315 320

Tyr Ala Gly Ser Glu Asn Gly Asn Leu Ile Lys Arg Asn Tyr Ala Trp  
 325 330 335

Gln Gln Thr Asp Asn Lys Thr Leu Ser Ser Asn Leu Thr Leu Asn Gly  
 340 345 350

Asp Tyr Thr Ile Gly Arg Phe Glu Asn His Leu Thr Val Gly Met Asp  
 355 360 365

Tyr Ser Arg Glu His Arg Asn Pro Thr Leu Gly Phe Ser Ser Ala Phe  
 370 375 380

Ser Ala Ser Ile Asn Pro Tyr Asp Arg Ala Ser Trp Pro Ala Ser Gly  
 385 390 395 400

Arg Leu Gln Pro Ile Leu Thr Gln Asn Arg His Lys Ala Asp Ser Tyr  
 405 410 415

Gly Ile Phe Val Gln Asn Ile Phe Ser Ala Thr Pro Asp Leu Lys Phe  
420 425 430

Val Leu Gly Gly Arg Tyr Asp Lys Tyr Thr Phe Asn Ser Glu Asn Lys  
435 440 445

Leu Thr Gly Ser Ser Arg Gln Tyr Ser Gly His Ser Phe Ser Pro Asn  
450 455 460

Ile Gly Ala Val Trp Asn Ile Asn Pro Val His Thr Leu Tyr Ala Ser  
465 470 475 480

Tyr Asn Lys Gly Phe Ala Pro Tyr Gly Gly Arg Gly Gly Tyr Leu Ser  
485 490 495

Ile Asp Thr Leu Ser Ser Ala Val Phe Asn Ala Asp Pro Glu Tyr Thr  
500 505 510

Arg Gln Tyr Glu Thr Gly Val Lys Ser Ser Trp Leu Asp Asp Arg Leu  
515 520 525

Ser Thr Thr Leu Ser Ala Tyr Gln Ile Glu Arg Phe Asn Ile Arg Tyr  
530 535 540

Arg Pro Asp Pro Lys Asn Asn Pro Tyr Ile Tyr Ala Val Ser Gly Lys  
545 550 555 560

His Arg Ser Arg Gly Val Glu Leu Ser Ala Ile Gly Gln Ile Ile Pro  
565 570 575

Lys Lys Leu Tyr Leu Arg Gly Ser Leu Gly Val Met Gln Ala Lys Val  
580 585 590

Val Glu Asp Lys Glu Asn Pro Asp Arg Val Gly Ile His Leu Asn Asn  
595 600 605

Thr Ser Asn Val Thr Gly Asn Leu Phe Phe Arg Tyr Thr Pro Thr Glu  
610 615 620

Asn Leu Tyr Gly Glu Ile Gly Val Thr Gly Thr Gly Lys Arg Tyr Gly  
625 630 635 640

Tyr Asn Ser Arg Asn Lys Glu Val Thr Thr Leu Pro Gly Phe Ala Arg  
645 650 655

Val Asp Ala Met Leu Gly Trp Asn His Lys Asn Val Asn Val Thr Phe  
660 665 670

Ala Ala Ala Asn Leu Leu Asn Gln Lys Tyr Trp Arg Ser Asp Ser Met  
 675 680 685

Pro Gly Asn Pro Arg Gly Tyr Thr Ala Arg Val Asn Tyr Arg Phe  
 690 695 700

<210> 53  
 <211> 693  
 <212> DNA  
 <213> *Neisseria meningitidis*

<400> 53  
 atgaacgct tcacctatc tctttccgac ggcttgtgca tcgaaatcga actcaaacgc 60  
 agtgccaaga aaaatctgat tctgcgcccc gtcaatatgc agacgggtcag catcaacgtc 120  
 ccacccctttt tcaagacca cgcgttagca aactggctgg cggcaaacga aacgattttg 180  
 cggaacacgc ttgctaaaaa gcccggtgat cctgtttccc acccaaaactt acccgagtgg 240  
 atttggatc ggggaataaa gaccaagctg gatacccaca gccaaagcca tatccgtatc 300  
 acgtcgctctg aaatcctgct tccccgaaaa gaaaccgccc cacaatcga ccacctgcgc 360  
 cgctctgtga acgaacgcgc ccgcgaatac ctgctgcccc gccttgaaaa acacgcagccc 420  
 gaaacaggac tgactccgc tgccacagac ctgagcaacg ccaaaacctt ttggggcgta 480  
 tgccgcccgc acaccggcat ccgcctcaac tggcggctga tcggcacgcc cgaatacgtc 540  
 gccgactatg tctgcatcca cgaactctgc caccctccgc accccgacca cagtcgcgc 600  
 ttttggcatt tggtagaacac gctgacgccc cataccgaca atgctaaaag ttgctgaag 660  
 gcgcacgggc gggaattgtt tgtgctgggg taa 693

<210> 54  
 <211> 230  
 <212> PRT  
 <213> *Neisseria meningitidis*

<400> 54  
 Met Lys Arg Phe Thr Tyr Thr Leu Ser Asp Gly Leu Cys Ile Glu Ile  
 1 5 10 15  
 Glu Leu Lys Arg Ser Ala Lys Lys Asn Leu Ile Leu Arg Pro Val Asn  
 20 25 30  
 Met Gln Thr Val Ser Ile Asn Val Pro Pro Phe Phe Gln Asp His Ala  
 35 40 45  
 Leu Ala Asn Trp Leu Ala Ala Asn Glu Thr Ile Leu Arg Asn Thr Leu  
 50 55 60  
 Ala Lys Met Pro Val His Pro Val Ser His Pro Asn Leu Pro Glu Trp  
 65 70 75 80

Ile Trp Tyr Arg Gly Ile Lys Thr Lys Leu Asp Thr His Ser Gln Ser  
85 90 95

His Ile Arg Ile Thr Ser Ser Glu Ile Leu Leu Pro Arg Lys Glu Thr  
100 105 110

Ala Ala Gln Ile Asp His Leu Arg Arg Leu Leu Asn Glu Arg Ala Arg  
115 120 125

Glu Tyr Leu Leu Pro Arg Leu Glu Lys His Ala Ala Glu Thr Gly Leu  
130 135 140

Thr Pro Ala Ala Thr Asp Leu Ser Asn Ala Lys Thr Phe Trp Gly Val  
145 150 155 160

Cys Arg Pro His Thr Gly Ile Arg Leu Asn Trp Arg Leu Ile Gly Thr  
165 170 175

Pro Glu Tyr Val Ala Asp Tyr Val Cys Ile His Glu Leu Cys His Leu  
180 185 190

Arg His Pro Asp His Ser Pro Arg Phe Trp His Leu Val Asn Thr Leu  
195 200 205

Thr Pro His Thr Asp Asn Ala Lys Ser Trp Leu Lys Ala His Gly Arg  
210 215 220

Glu Leu Phe Val Leu Gly  
225 230

<210> 55

<211> 546

<212> DNA

<213> *Neisseria meningitidis*

<400> 55

atgagcaaga ttattgtgct gaccgcaggc cacagcaaca ccgacccggg tgcgggtcaac 60  
ggaagcgacc gtgaggcgga cttggcgag gatatgcgca acattgtggc ttcaatcctg 120  
cgtaacgatt acggcctgac cggtaaaaac gacggcacgg gcaaaggcaa tatgccgctg 180  
cgcgaaaggc tcaagctgat tcgaggctcg gatgtggcga ttgagtttca caccaacgct 240  
gccgtcagca aagcggcgac aggcacatgaa gccttgagta ccgttaaaaa caaacgctgg 300  
tgtcaggtgt tgagcaaaag cggtgccaag aaaaccggct ggaacttcg cggcgaagac 360  
ggctttaaac ccgacaatgc gggccagcat tcgagcctgg cttatgcaca agccggcggc 420  
attgtgtttg agcctttttt catcagcaac gacactgatt tggccttggt taagacgact 480  
aaatggggca tctgccgcgc gattgaggac gcgattgcga tggaattggg ggcggcaaga 540  
gtatga 546

<210> 56  
 <211> 181  
 <212> PRT  
 <213> Neisseria meningitidis

<400> 56

Met	Ser	Lys	Ile	Ile	Val	Leu	Thr	Ala	Gly	His	Ser	Asn	Thr	Asp	Pro
1				5					10					15	
Gly	Ala	Val	Asn	Gly	Ser	Asp	Arg	Glu	Ala	Asp	Leu	Ala	Gln	Asp	Met
			20					25					30		
Arg	Asn	Ile	Val	Ala	Ser	Ile	Leu	Arg	Asn	Asp	Tyr	Gly	Leu	Thr	Val
	35						40					45			
Lys	Thr	Asp	Gly	Thr	Gly	Lys	Gly	Asn	Met	Pro	Leu	Arg	Glu	Ala	Val
	50					55					60				
Lys	Leu	Ile	Arg	Gly	Ser	Asp	Val	Ala	Ile	Glu	Phe	His	Thr	Asn	Ala
65					70				75					80	
Ala	Val	Ser	Lys	Ala	Ala	Thr	Gly	Ile	Glu	Ala	Leu	Ser	Thr	Val	Lys
			85						90					95	
Asn	Lys	Arg	Trp	Cys	Gln	Val	Leu	Ser	Lys	Ala	Val	Ala	Lys	Lys	Thr
		100						105					110		
Gly	Trp	Lys	Leu	Arg	Gly	Glu	Asp	Gly	Phe	Lys	Pro	Asp	Asn	Ala	Gly
	115					120						125			
Gln	His	Ser	Arg	Leu	Ala	Tyr	Ala	Gln	Ala	Gly	Gly	Ile	Val	Phe	Glu
130						135					140				
Pro	Phe	Phe	Ile	Ser	Asn	Asp	Thr	Asp	Leu	Ala	Leu	Phe	Lys	Thr	Thr
145				150					155					160	
Lys	Trp	Gly	Ile	Cys	Arg	Ala	Ile	Ala	Asp	Ala	Ile	Ala	Met	Glu	Leu
			165					170					175		
Gly	Ala	Ala	Arg	Val											
			180												

<210> 57  
 <211> 237  
 <212> DNA  
 <213> Neisseria meningitidis



<400> 57  
 atgcgatttt tggatatatt taaaaaccca gcgacaggca atgtgtcgca ctgaaaactg 60  
 tgggcaaacg ttgcctgcgc ggcggggacg gtttaagttt tgatgctgcc cgaccgcgtc 120  
 gcggagattt ggcgcgtgta tttgggcatt gtcggcggtc atgcgggtgc gcgttcgttg 180  
 gtcagcgtca aacgtcagga ggtcgagaat gaatctcgtg aaactgctgg cgaataa 237

<210> 58  
 <211> 78  
 <212> PRT  
 <213> Neisseria meningitidis

<400> 58  
 Met Arg Ile Leu Asp Ile Phe Lys Asn Pro Ala Thr Gly Asn Val Ser  
 1 5 10 15

His Ser Lys Leu Trp Ala Asn Val Ala Cys Ala Ala Gly Thr Val Lys  
 20 25 30

Phe Val Met Leu Pro Asp Pro Ser Ala Glu Ile Trp Ala Val Tyr Leu  
 35 40 45

Gly Ile Val Gly Gly Tyr Ala Val Ala Arg Ser Leu Val Ser Val Lys  
 50 55 60

Arg Gln Glu Val Glu Asn Glu Ser Arg Glu Thr Ala Gly Glu  
 65 70 75

<210> 59  
 <211> 468  
 <212> DNA  
 <213> Neisseria meningitidis

<400> 59  
 atgcggtggc gcgttcgttg gtcagcgtca aacgtcagga ggtcgagaat gaatctcgtg 60  
 aaactgctgg cgaataaactg gcaaccgatt gccatcatcg cgcttgcgtg caccgggttg 120  
 gcggtgtcgc accatcaaagg ctacaagtcg gcttttcgca agcagcaggc ggtcattgag 180  
 aaaaatgaagc gcgacaaggc gcaagccctg ctgttgcgtg ctcaaaacta gccccgcgaa 240  
 ctggaacagg cgcgtgcgga agctaaaaaa tatgaagtca aggcgcacgc cgtcggcatg 300  
 gctttggcga aaaaacaggc ggaagtcagc cgtctgaaaa cggaataataa aaaggaaatc 360  
 gaaaatgtcc ttactcaaga ccgtaaaaat gcaggcggcg gttgtattga cggtttggc 420  
 catcacggct tgcagctcta caagcgcgcc ctcggctacg gaaattaa 468

<210> 60  
 <211> 155  
 <212> PRT  
 <213> Neisseria meningitidis

&lt;400&gt; 60

Met Arg Trp Arg Val Arg Trp Ser Ala Ser Asn Val Arg Arg Ser Arg  
 1 5 10 15

Met Asn Leu Val Lys Leu Leu Ala Asn Asn Trp Gln Pro Ile Ala Ile  
 20 25 30

Ile Ala Leu Val Gly Thr Gly Leu Ala Val Ser His His Gln Gly Tyr  
 35 40 45

Lys Ser Ala Phe Ala Lys Gln Gln Ala Val Ile Glu Lys Met Lys Arg  
 50 55 60

Asp Lys Ala Gln Ala Leu Leu Leu Ser Ala Gln Asn Tyr Ala Arg Glu  
 65 70 75 80

Leu Glu Gln Ala Arg Ala Glu Ala Lys Lys Tyr Glu Val Lys Ala His  
 85 90 95

Ala Val Gly Met Ala Leu Ala Lys Lys Gln Ala Glu Val Ser Arg Leu  
 100 105 110

Lys Thr Glu Asn Lys Lys Glu Ile Glu Asn Val Leu Thr Gln Asp Arg  
 115 120 125

Lys Asn Ala Gly Gly Gly Cys Ile Asp Gly Phe Gly His His Gly Leu  
 130 135 140

Gln Leu Tyr Lys Arg Ala Leu Gly Tyr Gly Asn  
 145 150 155

&lt;210&gt; 61

&lt;211&gt; 306

&lt;212&gt; DNA

<213> *Neisseria meningitidis*

&lt;400&gt; 61

atgtccttac tcaagaccgt aaaaatgcag gcggcggttg tattgacggc ttgggccatc 60  
 acggccttgca gctctacaag cgcgccctcg gctacggaaa ttaaggttgt cgaaaaggcg 120  
 gtcattgccga caccgcctgc cgcgttgatg gtcgcgccgg tgcgcccgaa tccgcgcgaa 180  
 gacggcaaga cggccacgct gttggaacac gccgccgagt ttggcggcta tgttgccgaa 240  
 cttgaaaacc aaaaatcaggc ttggcgcgac tgggggggca atcactcccg caaagtcgga 300  
 aactga 306

&lt;210&gt; 62

&lt;211&gt; 101

&lt;212&gt; PRT

<213> *Neisseria meningitidis*

&lt;400&gt; 62

Met Ser Leu Leu Lys Thr Val Lys Met Gln Ala Ala Val Val Leu Thr  
 1 5 10 15

Ala Leu Ala Ile Thr Ala Cys Ser Ser Thr Ser Ala Pro Ser Ala Thr  
 20 25 30

Glu Ile Lys Val Val Glu Lys Ala Val Met Pro Thr Pro Pro Ala Ala  
 35 40 45

Leu Met Val Ala Pro Val Arg Pro Asn Pro Pro Lys Asp Gly Lys Thr  
 50 55 60

Ala Thr Leu Leu Glu His Ala Ala Glu Phe Gly Gly Tyr Val Ala Glu  
 65 70 75 80

Leu Glu Asn Gln Asn Gln Ala Trp Arg Asp Trp Ala Gly Asn His Ser  
 85 90 95

Arg Lys Val Gly Asn  
 100

&lt;210&gt; 63

&lt;211&gt; 348

&lt;212&gt; DNA

<213> *Neisseria meningitidis*

&lt;400&gt; 63

gtgctggcag ttttctctgc tgggttagcc ttccgacctga gcgatgatt catggttggc 60  
 tgctttcaaa cgccaacggt attcgccctt tgcgtcttta tagatttcaa aatacataag 120  
 gtttctccta tgaatgagta cagcttttct taccgcttta acggcaagtc ctggctcattg 180  
 agcatttggg cggacaaccc tgaagaagcc agggcgaaat ttccgggctgc acgagaaaaa 240  
 gcgcactatg acggcgaaag tgtagcaaag gtttatacat ttgtaaatat ttctgtgggtt 300  
 aagaaattgt acaagcggac aaaatattta atgggtatca aagaatga 348

&lt;210&gt; 64

&lt;211&gt; 115

&lt;212&gt; PRT

<213> *Neisseria meningitidis*

&lt;400&gt; 64

Val Leu Ala Val Leu Leu Ala Gly Val Ala Phe Ala Leu Ser Asp Asp  
 1 5 10 15

Phe Met Val Gly Cys Phe Gln Thr Pro Thr Val Phe Ala Phe Cys Val  
20 25 30

Phe Ile Asp Phe Lys Ile His Lys Val Ser Pro Met Asn Glu Tyr Thr  
35 40 45

Phe Ser Tyr Arg Phe Asn Gly Lys Ser Trp Ser Leu Ser Ile Trp Ala  
50 55 60

Asp Asn Pro Glu Glu Ala Arg Ala Lys Phe Arg Ala Ala Arg Glu Asn  
65 70 75 80

Ala His Tyr Asp Gly Glu Val Val Ala Lys Val Tyr Thr Phe Val Asn  
85 90 95

Ile Ser Trp Val Lys Lys Leu Tyr Lys Arg Thr Lys Tyr Leu Met Gly  
100 105 110

Ile Lys Glu  
115

<210> 65

<211> 1404

<212> DNA

<213> Neisseria meningitidis

<400> 65

atgacattgc tcaatcctaata gataatgcaa gattacggta ttcccggttg cctgacactg 60  
acgccctatt tgcaacatga actatttttcg gctatgaaat cctatttttc caaatatatt 120  
ctaccctgtt cactttttac cttgccacta tccctttccc catccgtttc ggctttttacg 180  
ctgacctgaag catggcgggc ggccgacgaa cattcggtg attttcaagc gtcccattac 240  
cagcgtgatg cagtgcgcgc acggcaacaa caagccaagg ccgcatctct tcccattgta 300  
tccgccaatg ccagctacca gcgccagccg ccctcgattt cttccaccgc cgaacacagc 360  
ggatggagcg tgcaggtggg acaaacctta ttgacgctg ccaaatgttc acaatccgc 420  
caaagcaggt tcgatacgca ggctgcagaa cagcggtttc atgcggcacg cgaagaattg 480  
ctgttgaaag ttgccgaaag ttatttcaac gttttactca gccgagacac cggttgcgc 540  
catgcggcgg aaaaagaggc ttatgcccag caggtaaagg aggcgcaggc ttatttcaat 600  
aaaggtgctg ccaccgcgct ggatattcac gaagccaaa cgggttacga caatgccctg 660  
gcccaagaaa tcgccgtatt ggctgagaaa caaacctatg aaacacagtt gaacgactac 720  
accggcctgg acagcaaaac aatcgaggcc atagataccg ccaacctgtt ggcacgctat 780  
ctgcccaagc tggaaacgtta cagtctggat gaatggcagc gcattgcctt atccaacaat 840  
catgaatacc ggatgcagca gcttgccctg caaagcagcg gacaggcgct tcgggcagca 900  
cagaacagcc gctatccacc cgtttctgcc catgtcgctt atcagaataa cctctacact 960  
tcattctgccc agaataatga ctaccactat cggggcaaa ggatgagcgt cggcgtagct 1020  
ttgaatttgc cgctttatgc cggcgagaaa ttgtcgggca aaatccatga agccgaagcg 1080  
caatacgggg ctgccgaagc acagctgacc gcaaccgagc ggcacatcaa actcgccgta 1140  
cgccaggctt ataccgaaag cggtcggcgc cgttaccaaa tcattggcgca agaaccgggt 1200

ttggaaagca gccgtttgaa actgaaatcg accgaaaccg gccacaata cggcatccgc 1260  
 aaccggctgg aagtaatacg ggcgcggcag gaagtcgccc aagcagaaca gaaactggct 1320  
 caagcacggg ataaattcat gctgccttat ttgcgcttgg tgaaagagag cgggttaggg 1380  
 ttggaaacgg tatttgcgga ataa 1404

<210> 66

<211> 467

<212> PRT

<213> Neisseria meningitidis

<400> 66

Met Thr Leu Leu Asn Leu Met Ile Met Gln Asp Tyr Gly Ile Ser Val  
 1 5 10 15

Cys Leu Thr Leu Thr Pro Tyr Leu Gln His Glu Leu Phe Ser Ala Met  
 20 25 30

Lys Ser Tyr Phe Ser Lys Tyr Ile Leu Pro Val Ser Leu Phe Thr Leu  
 35 40 45

Pro Leu Ser Leu Ser Pro Ser Val Ser Ala Phe Thr Leu Pro Glu Ala  
 50 55 60

Trp Arg Ala Ala Gln Gln His Ser Ala Asp Phe Gln Ala Ser His Tyr  
 65 70 75 80

Gln Arg Asp Ala Val Arg Ala Arg Gln Gln Gln Ala Lys Ala Ala Phe  
 85 90 95

Leu Pro His Val Ser Ala Asn Ala Ser Tyr Gln Arg Gln Pro Pro Ser  
 100 105 110

Ile Ser Ser Thr Arg Glu Thr Gln Gly Trp Ser Val Gln Val Gly Gln  
 115 120 125

Thr Leu Phe Asp Ala Ala Lys Phe Ala Gln Tyr Arg Gln Ser Arg Phe  
 130 135 140

Asp Thr Gln Ala Ala Glu Gln Arg Phe Asp Ala Ala Arg Glu Glu Leu  
 145 150 155 160

Leu Leu Lys Val Ala Glu Ser Tyr Phe Asn Val Leu Leu Ser Arg Asp  
 165 170 175

Thr Val Ala Ala His Ala Ala Glu Lys Glu Ala Tyr Ala Gln Gln Val  
 180 185 190

Arg Gln Ala Gln Ala Leu Phe Asn Lys Gly Ala Ala Thr Ala Leu Asp

195

200

205

Ile His Glu Ala Lys Ala Gly Tyr Asp Asn Ala Leu Ala Gln Glu Ile  
210 215 220

Ala Val Leu Ala Glu Lys Gln Thr Tyr Glu Asn Gln Leu Asn Asp Tyr  
225 230 235 240

Thr Gly Leu Asp Ser Lys Gln Ile Glu Ala Ile Asp Thr Ala Asn Leu  
245 250 255

Leu Ala Arg Tyr Leu Pro Lys Leu Glu Arg Tyr Ser Leu Asp Glu Trp  
260 265 270

Gln Arg Ile Ala Leu Ser Asn Asn His Glu Tyr Arg Met Gln Gln Leu  
275 280 285

Ala Leu Gln Ser Ser Gly Gln Ala Leu Arg Ala Ala Gln Asn Ser Arg  
290 295 300

Tyr Pro Thr Val Ser Ala His Val Gly Tyr Gln Asn Asn Leu Tyr Thr  
305 310 315 320

Ser Ser Ala Gln Asn Asn Asp Tyr His Tyr Arg Gly Lys Gly Met Ser  
325 330 335

Val Gly Val Gln Leu Asn Leu Pro Leu Tyr Thr Gly Gly Glu Leu Ser  
340 345 350

Gly Lys Ile His Glu Ala Glu Ala Gln Tyr Gly Ala Ala Glu Ala Gln  
355 360 365

Leu Thr Ala Thr Glu Arg His Ile Lys Leu Ala Val Arg Gln Ala Tyr  
370 375 380

Thr Glu Ser Gly Ala Ala Arg Tyr Gln Ile Met Ala Gln Glu Arg Val  
385 390 395 400

Leu Glu Ser Ser Arg Leu Lys Leu Lys Ser Thr Glu Thr Gly Gln Gln  
405 410 415

Tyr Gly Ile Arg Asn Arg Leu Glu Val Ile Arg Ala Arg Gln Glu Val  
420 425 430

Ala Gln Ala Glu Gln Lys Leu Ala Gln Ala Arg Tyr Lys Phe Met Leu  
435 440 445

Ala Tyr Leu Arg Leu Val Lys Glu Ser Gly Leu Gly Leu Glu Thr Val

450

455

460

Phe Ala Glu  
465

<210> 67  
<211> 1404  
<212> DNA  
<213> *Neisseria meningitidis*

<400> 67  
atgacattgc tcaatctaata gataatgcaa gattacggta ttccggttg cctgacactg 60  
acgcccattt tgcaaatgaa actatatttc gctatgaaat cctatttttc caaatatatac 120  
ctaccgcttt cactttttac ctggccacta tccctttccc catcggtttc ggctttttacg 180  
ctgcctgaag catggcgggc ggccgagcaa cattcggctg attttcaagc gtcccattac 240  
cagcgtgatg cagtgcggcg acggcaacaa caagccaagg ccgcattcct tccccatgta 300  
tcgcgcaatg ccagctacca gcgccagccg ccattcgatt ctccaccacc cgaacacag 360  
ggatggagcg tgcaggtggg acaaacctta ttgacgctg ccaaatattgc acaataccgc 420  
caaaagcagg tcgatacgca ggctgcagaa cagcggttcg atgcggcgac cgaagaattg 480  
ctgttgaaaag ttgccgaaa ttatttcaac gttttactca gccgagacac cggtggccgcc 540  
catgcggcgg aaaaagaggc ttatgcccgag caggttaaggc aggcgcaggc ttatttcaat 600  
aaaggtgctg ccaccgcgct ggatattcac gaagccaaa cgggttacga caatgccctg 660  
gcccaagaaa tcgcgctatt ggctgagaaa caaacctatg aaaccaggt gaacgactac 720  
accggccttg acagcaaaac aatcgaggcc atagataccg ccaacctgtt ggcacgctat 780  
ctgcccgaag tggaaacgta cagtcgggat gaatggcagc gcattgcctt attccaaat 840  
catgaatacc ggatgcagca gcttgccctg caaagcagcg gacaggcgct tcgggcagca 900  
cagaacagcc gctatccac cgctttctgcc catgtcggct atcagaataa cctctacact 960  
tcattctgcg agaataatga ctaccactat cggggcaaa ggatgagcgt cggcgtagac 1020  
ttgaatttgc cgctttatc cgccggagaa ttgtcgggca aaatccatga agccgaagcg 1080  
caatacgggg ctgccgaagc acagctgacc gcaaccgagc ggccacatcaa actcggcgta 1140  
cgccaggctt ataccgaaa cggtcggcgc gttaccaaa tcatggcgca agaaccgggt 1200  
ttggaagaca gccgtttgaa actgaaatcg accgaaaccg gccacaata cggcatccgc 1260  
aaccggctgg aagtaatacg ggcgcggcag gaagtcgccc aagcagaaca gaaactggct 1320  
caagcagcgt ataaattcat gctgccttat ttgcgcttgg tgaagagag cgggttaggg 1380  
ttggaacgg tatttgcgga ataa 1404

<210> 68  
<211> 467  
<212> PRT  
<213> *Neisseria meningitidis*

<400> 68  
Met Thr Leu Leu Asn Leu Met Ile Met Gln Asp Tyr Gly Ile Ser Val  
1 5 10 15

Cys Leu Thr Leu Thr Pro Tyr Leu His Gln Leu Phe Ser Ala Met  
20 25 30

Lys Ser Tyr Phe Ser Lys Tyr Ile Leu Pro Val Ser Leu Phe Thr Leu  
 35 40 45  
 Pro Leu Ser Leu Ser Pro Ser Val Ser Ala Phe Thr Leu Pro Glu Ala  
 50 55 60  
 Trp Arg Ala Ala Gln Gln His Ser Ala Asp Phe Gln Ala Ser His Tyr  
 65 70 75 80  
 Gln Arg Asp Ala Val Arg Ala Arg Gln Gln Gln Ala Lys Ala Ala Phe  
 85 90 95  
 Leu Pro His Val Ser Ala Asn Ala Ser Tyr Gln Arg Gln Pro Pro Ser  
 100 105 110  
 Ile Ser Ser Thr Arg Glu Thr Gln Gly Trp Ser Val Gln Val Gly Gln  
 115 120 125  
 Thr Leu Phe Asp Ala Ala Lys Phe Ala Gln Tyr Arg Gln Ser Arg Phe  
 130 135 140  
 Asp Thr Gln Ala Ala Glu Gln Arg Phe Asp Ala Ala Arg Glu Glu Leu  
 145 150 155 160  
 Leu Leu Lys Val Ala Glu Ser Tyr Phe Asn Val Leu Leu Ser Arg Asp  
 165 170 175  
 Thr Val Ala Ala His Ala Ala Glu Lys Glu Ala Tyr Ala Gln Gln Val  
 180 185 190  
 Arg Gln Ala Gln Ala Leu Phe Asn Lys Gly Ala Ala Thr Ala Leu Asp  
 195 200 205  
 Ile His Glu Ala Lys Ala Gly Tyr Asp Asn Ala Leu Ala Gln Glu Ile  
 210 215 220  
 Ala Val Leu Ala Glu Lys Gln Thr Tyr Glu Asn Gln Leu Asn Asp Tyr  
 225 230 235 240  
 Thr Gly Leu Asp Ser Lys Gln Ile Glu Ala Ile Asp Thr Ala Asn Leu  
 245 250 255  
 Leu Ala Arg Tyr Leu Pro Lys Leu Glu Arg Tyr Ser Leu Asp Glu Trp  
 260 265 270  
 Gln Arg Ile Ala Leu Ser Asn Asn His Glu Tyr Arg Met Gln Gln Leu  
 275 280 285



Ala Leu Gln Ser Ser Gly Gln Ala Leu Arg Ala Ala Gln Asn Ser Arg  
 290 295 300

Tyr Pro Thr Val Ser Ala His Val Gly Tyr Gln Asn Asn Leu Tyr Thr  
 305 310 315 320

Ser Ser Ala Gln Asn Asn Asp Tyr His Tyr Arg Gly Lys Gly Met Ser  
 325 330 335

Val Gly Val Gln Leu Asn Leu Pro Leu Tyr Thr Gly Gly Glu Leu Ser  
 340 345 350

Gly Lys Ile His Glu Ala Glu Ala Gln Tyr Gly Ala Ala Glu Ala Gln  
 355 360 365

Leu Thr Ala Thr Glu Arg His Ile Lys Leu Ala Val Arg Gln Ala Tyr  
 370 375 380

Thr Glu Ser Gly Ala Ala Arg Tyr Gln Ile Met Ala Gln Glu Arg Val  
 385 390 395 400

Leu Glu Ser Ser Arg Leu Lys Leu Lys Ser Thr Glu Thr Gly Gln Gln  
 405 410 415

Tyr Gly Ile Arg Asn Arg Leu Glu Val Ile Arg Ala Arg Gln Glu Val  
 420 425 430

Ala Gln Ala Glu Gln Lys Leu Ala Gln Ala Arg Tyr Lys Phe Met Leu  
 435 440 445

Ala Tyr Leu Arg Leu Val Lys Glu Ser Gly Leu Gly Leu Glu Thr Val  
 450 455 460

Phe Ala Glu  
 465

<210> 69

<211> 1400

<212> DNA

<213> *Neisseria meningitidis*

<400> 69

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 ccgtttcaact ttttaccttg ccactatccc ttccccatc cgtttcggct ttacgcgtgc 180  
 ctgaagcatg gcgggcggcg cagcaacatt cggctgattt tcaagcgtcc cattaccagc 240

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gtgatgcagt ggcgcgacgg caacaacaag ccaaggccgc attccttccc catgtatccg 300  
 ccaatgccag ctaccagcgc cagccgccat cgatttcttc caccgcgcaa acacagggat 360  
 ggagcgtgca ggtgggacaa accttatttg actctgcaa atttgcacaa taccgcaaaa 420  
 gcaggttcga tacgcaggct gcagaacagc gtttcgatgc ggcacgcgaa gaattgctgt 480  
 tgaaagtgtc gaaagtatt ttcaacgttt tactcagccg agacaccgtt gccgcccatg 540  
 cggcggaaaa agaggcttat gcccgagcagg taaggcaggc gcaggcttta ttcaataaag 600  
 gtgctgccac cgctgtagat attcaagaa ccaagccggg ttacgacaat gccctggccc 660  
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 gcctggacag caaacaatc gaggccatag ataccgcaaa cctgttggca cgctatctgc 780  
 ccaagctgga acgttacagt ctggatgaat ggcagcgcgt tgcctttacc aacaatcatg 840  
 aataccggat gcagcagctt gccctgcaaa gcagcggaca ggcgcttcgg gcagcacaga 900  
 acagccgcta tcccaccgtt ttctgcccatt tcggctatca gaataacctc tacacttcat 960  
 ctgcgcagaa taatgactac cactatcggg gcaaaggat gagcgtcggg gtacagtgtg 1020  
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 accgggctgc cgaagcacag ctgaccgcaa ccgagcggca catcaaaact gccgtacgac 1140  
 aggtttatac cgaagcgggt gcggcgcggt accaaatcat ggcgcaagaa cgggttttgg 1200  
 aaagcagcgc tttgaaactg aaatcgaccg aaaccggcca acaatcaggg atccgcaacc 1260  
 ggctggaagt aatacgggag cggcagggaag tcgcccgaag agaacagaaa ctggctcaag 1320  
 caggtataa attcatgctg cttatttgc gcttggtgaa agagagcggg ttagggttgg 1380  
 aaacgggtatt tgcggaataa 1400

<210> 70

<211> 450

<212> PRT

<213> Neisseria meningitidis

<400> 70

Met Thr Leu Leu Asn Leu Ile Cys Lys Ile Thr Val Phe Pro Phe Ala  
 1 5 10 15

His Arg Pro Ile Cys Asn Met Asn Tyr Phe Arg Leu Asn Pro Ile Phe  
 20 25 30

Pro Asn Ile Ser Tyr Pro Phe His Phe Leu Pro Cys His Tyr Pro Phe  
 35 40 45

Pro His Pro Phe Arg Leu Leu Arg Cys Leu Lys His Gly Gly Arg Arg  
 50 55 60

Ser Asn Ile Arg Leu Ile Phe Lys Arg Pro Ile Thr Ser Val Met Gln  
 65 70 75 80

Cys Ala His Gly Asn Asn Lys Pro Arg Pro His Ser Phe Pro Met Tyr  
 85 90 95

Pro Pro Met Pro Ala Thr Ser Ala Ser Arg His Arg Phe Leu Pro Pro  
 100 105 110

Ala Lys His Arg Asp Gly Ala Cys Arg Trp Asp Lys Pro Tyr Leu Thr  
 115 120 125

Leu Pro Asn Leu His Asn Thr Ala Lys Ala Gly Ser Ile Arg Arg Leu  
 130 135 140

Gln Asn Ser Val Ser Met Arg His Ala Lys Asn Cys Cys Lys Leu Pro  
 145 150 155 160

Lys Val Ile Ser Thr Phe Tyr Ser Ala Glu Thr Pro Leu Pro Pro Met  
 165 170 175

Arg Arg Lys Lys Arg Leu Met Pro Ser Arg Gly Arg Arg Arg Leu Tyr  
 180 185 190

Ser Ile Lys Val Leu Pro Pro Arg Ile Phe Thr Lys Pro Lys Pro Val  
 195 200 205

Thr Thr Met Pro Trp Pro Lys Lys Ser Pro Tyr Trp Leu Arg Asn Lys  
 210 215 220

Pro Met Lys Thr Ser Thr Thr Thr Pro Ala Trp Thr Ala Asn Lys Ser  
 225 230 235 240

Arg Pro Ile Pro Pro Thr Cys Trp His Ala Ile Cys Pro Ser Trp Asn  
 245 250 255

Val Thr Val Trp Met Asn Gly Ser Ala Leu Pro Tyr Pro Thr Ile Met  
 260 265 270

Asn Thr Gly Cys Ser Ser Leu Pro Cys Lys Ala Ala Asp Arg Arg Phe  
 275 280 285

Gly Gln His Arg Thr Ala Ala Ile Pro Pro Phe Leu Pro Met Ser Ala  
 290 295 300

Ile Arg Ile Thr Ser Thr Leu His Leu Arg Arg Ile Met Thr Thr Thr  
 305 310 315 320

Ile Gly Ala Lys Gly Ala Ser Ala Tyr Ser Ile Cys Arg Phe Ile Pro  
 325 330 335

Ala Glu Asn Cys Arg Ala Lys Ser Met Lys Pro Lys Arg Asn Thr Gly  
 340 345 350

Leu Pro Lys His Ser Pro Gln Pro Ser Gly Thr Ser Asn Ser Pro Tyr  
 355 360 365

Ala Arg Leu Ile Pro Lys Ala Val Arg Arg Val Thr Lys Ser Trp Arg  
370 375 380

Lys Asn Gly Phe Trp Lys Ala Ala Val Asn Asn Arg Pro Lys Pro Ala  
385 390 395 400

Asn Asn Thr Ala Ser Ala Thr Gly Trp Lys Tyr Gly Arg Gly Arg Lys  
405 410 415

Ser Pro Lys Gln Asn Arg Asn Trp Leu Lys His Gly Ile Asn Ser Cys  
420 425 430

Trp Leu Ile Cys Ala Trp Lys Arg Ala Gly Gly Trp Lys Arg Tyr Leu  
435 440 445

Arg Asn  
450

<210> 71

<211> 1404

<212> DNA

<213> Neisseria meningitidis

<400> 71

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acgccctatt tgcaacatga actatatttcg gctatgaaat cctatattttc caaatatatac 120  
ctaccgggtt cactttttac cttgccacta tccctttccc catccgtttc ggctttttacg 180  
ctgctgaag catggcgggc ggccgagcaa cattcggctg attttcaacg gtcccattac 240  
cagcgtgatg cagtgcgcgc acggcaacaa caagccaagg ccgcattcct tccccatgta 300  
tcgcgcaatg ccagctacca gcgccagccg ccacgtgatt ctccaccgc cgaacacacag 360  
ggatggagcg tgcaggtggg acaaacctta tttagcgtg ccaaatattgc acaatcccg 420  
caaaagcaggt tcgatacgca ggctgcagaa cagcgtttcg atgcggcagc cgaagaattg 480  
ctgttgaaaag ttgccgaaag ttatttcaac gttttactca gccgagacac cgttgcggcc 540  
catgcggcgg aaaaagagcg ttatgcccg caggtaaggc aggcgcaggc ttatttcaat 600  
aaaggtgctg ccaccgcgct ggatattcac gaagccaaag ccggtttacga caatgccttg 660  
gcccaagaaa tcgccgtatt ggctgagaaa caaacctatg aaaaccagtt gaacgactac 720  
accgacctgg atagcaaaaca aatcgaggcc atagataccg ccaacctgtt ggcacgctat 780  
ctgcccaagc tggaaagctta cagtctggat gaatggcagc gcattgcctt atccaacaat 840  
catgaatacc ggatgcagca gcttgccctg caaagcagcg gacagcgctt tcgggcagca 900  
cagaacagcc gctatcccac cgtttctgccc catgtcggct atcagaataa cctctacact 960  
tcactctgcg agaataatga ctaccactat cggggcgaag ggatgagcgt cggcgtacag 1020  
ttgaatttgc cgttttatac cggcggagaa ttgtcgggca aaatccatga agccgaagcg 1080  
caatacgggg ccgccgaagc acagctgacc gcaaccgagc ggcacatcaa actcgcgcta 1140  
cgccaggett ataccgaaag cgggtcggcg cggttaccaaa tcattggcga agaacgggtt 1200  
ttggaaagca gccgtttgaa actgaaatcg accgaaaccg gccaaacaata cggcatccgc 1260  
aacccggtgg aagtaatacg ggcgcggcag gaagtcgccc aagcagaaca gaaactggct 1320  
caagcacggt ataaattcat gctggcttat ttgcgcttgg tgaagagagag cgggttaggg 1380

ttggaacgg tatttgcgga ataa

1404

&lt;210&gt; 72

&lt;211&gt; 467

&lt;212&gt; PRT

&lt;213&gt; Neisseria meningitidis

&lt;400&gt; 72

Met	Thr	Leu	Leu	Asn	Leu	Met	Ile	Met	Gln	Asp	Tyr	Gly	Ile	Ser	Val
1				5					10					15	

Cys	Leu	Thr	Leu	Thr	Pro	Tyr	Leu	Gln	His	Glu	Leu	Phe	Ser	Ala	Met
			20					25					30		

Lys	Ser	Tyr	Phe	Ser	Lys	Tyr	Ile	Leu	Pro	Val	Ser	Leu	Phe	Thr	Leu
		35					40					45			

Pro	Leu	Ser	Leu	Ser	Pro	Ser	Val	Ser	Ala	Phe	Thr	Leu	Pro	Glu	Ala
	50					55					60				

Trp	Arg	Ala	Ala	Gln	Gln	His	Ser	Ala	Asp	Phe	Gln	Ala	Ser	His	Tyr
65				70						75				80	

Gln	Arg	Asp	Ala	Val	Arg	Ala	Arg	Gln	Gln	Gln	Ala	Lys	Ala	Ala	Phe
			85						90					95	

Leu	Pro	His	Val	Ser	Ala	Asn	Ala	Ser	Tyr	Gln	Arg	Gln	Pro	Pro	Ser
		100							105					110	

Ile	Ser	Ser	Thr	Arg	Glu	Thr	Gln	Gly	Trp	Ser	Val	Gln	Val	Gly	Gln
		115					120					125			

Thr	Leu	Phe	Asp	Ala	Ala	Lys	Phe	Ala	Gln	Tyr	Arg	Gln	Ser	Arg	Phe
	130					135					140				

Asp	Thr	Gln	Ala	Ala	Glu	Gln	Arg	Phe	Asp	Ala	Ala	Arg	Glu	Glu	Leu
145					150					155				160	

Leu	Leu	Lys	Val	Ala	Glu	Ser	Tyr	Phe	Asn	Val	Leu	Leu	Ser	Arg	Asp
			165						170					175	

Thr	Val	Ala	Ala	His	Ala	Ala	Glu	Lys	Glu	Ala	Tyr	Ala	Gln	Gln	Val
		180						185					190		

Arg	Gln	Ala	Gln	Ala	Leu	Phe	Asn	Lys	Gly	Ala	Ala	Thr	Ala	Leu	Asp
	195						200					205			

Ile	His	Glu	Ala	Lys	Ala	Gly	Tyr	Asp	Asn	Ala	Leu	Ala	Gln	Glu	Ile
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

210	215	220
Ala Val Leu Ala Glu Lys Gln Thr Tyr Glu Asn Gln Leu Asn Asp Tyr		
225	230	240
Thr Asp Leu Asp Ser Lys Gln Ile Glu Ala Ile Asp Thr Ala Asn Leu		
245	250	255
Leu Ala Arg Tyr Leu Pro Lys Leu Glu Arg Tyr Ser Leu Asp Glu Trp		
260	265	270
Gln Arg Ile Ala Leu Ser Asn Asn His Glu Tyr Arg Met Gln Gln Leu		
275	280	285
Ala Leu Gln Ser Ser Gly Gln Ala Leu Arg Ala Ala Gln Asn Ser Arg		
290	295	300
Tyr Pro Thr Val Ser Ala His Val Gly Tyr Gln Asn Asn Leu Tyr Thr		
305	310	320
Ser Ser Ala Gln Asn Asn Asp Tyr His Tyr Arg Gly Lys Gly Met Ser		
325	330	335
Val Gly Val Gln Leu Asn Leu Pro Leu Tyr Thr Gly Gly Glu Leu Ser		
340	345	350
Gly Lys Ile His Glu Ala Glu Ala Gln Tyr Gly Ala Ala Glu Ala Gln		
355	360	365
Leu Thr Ala Thr Glu Arg His Ile Lys Leu Ala Val Arg Gln Ala Tyr		
370	375	380
Thr Glu Ser Gly Ala Ala Arg Tyr Gln Ile Met Ala Gln Glu Arg Val		
385	390	400
Leu Glu Ser Ser Arg Leu Lys Leu Lys Ser Thr Glu Thr Gly Gln Gln		
405	410	415
Tyr Gly Ile Arg Asn Arg Leu Glu Val Ile Arg Ala Arg Gln Glu Val		
420	425	430
Ala Gln Ala Glu Gln Lys Leu Ala Gln Ala Arg Tyr Lys Phe Met Leu		
435	440	445
Ala Tyr Leu Arg Leu Val Lys Glu Ser Gly Leu Gly Leu Glu Thr Val		
450	455	460
Phe Ala Glu		

465

&lt;210&gt; 73

&lt;211&gt; 1404

&lt;212&gt; DNA

<213> *Neisseria meningitidis*

&lt;400&gt; 73

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ctacccgttt cactttttac cttgccacta tccctttccc catccgtttc ggcttttacg 180
ctgectgaag catggcgggc ggccgagcaa cattcgctg attttcaagc gtcccattac 240
cagcgtgatg cagtgcgcgc acggcaacaa caagccaagg ccgcattcct tccccatgta 300
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ggatggagcg tgcaggtggg acaaacctta ttgacgctg ccaaatttgc acaataccgc 420
caaagcaggt tcgatacgca ggctgcagaa cagcgtttcg atgcggcagc cgaagaattg 480
ctgttgaaag ttgccgaaag ttatttcaac gttttactca gccgagacac cgttgcgcgc 540
catgcgcgcg aaaaagaggg ttatgccag caggttaagg aggcgcaggc ttatttcaat 600
aaaggtgctg ccaccgcgct ggatattcac gaagccaaag ccggttacga caatgccctg 660
gcccaagaaa tcgccgtatt ggctgagaaa caaacctatg aaaaccagtt gaacgactac 720
accgacctgg atagcaaaaca aatcgaggcc atagataccg ccaacctgtt ggcacgctat 780
ctgcccgaag tggaaagtta cagtctggat gaatggcagc gcattgcctt atccaacaat 840
catgaatacc ggaatgcagc gcttgcctcg caaagcagcg gacaggcgct tcgggcagca 900
cagaacagcc gctatcccac cgtttctgcc catgtcgct atcagaataa cctctacact 960
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aaccggctgg aagtaatacg ggcgcggcag gaagtcgccc aagcagaaca gaaactggct 1320
caagcacggt ataaattcat gctggcttat ttgcgcttg tgaagagag cgggttaggg 1380
ttggaacggt tatttgcgga ataa 1404

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&lt;210&gt; 74

&lt;211&gt; 467

&lt;212&gt; PRT

<213> *Neisseria meningitidis*

&lt;400&gt; 74

```

Met Met Thr Leu Asn Leu Met Ile Met Gln Asp Tyr Gly Ile Ser Val
  1                      5                      10                     15

```

```

Cys Leu Thr Leu Thr Pro Tyr Leu Gln His Glu Leu Phe Ser Ala Met
      20                      25                     30

```

```

Lys Ser Tyr Phe Ser Lys Tyr Ile Leu Pro Val Ser Leu Phe Thr Leu
      35                      40                     45

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Pro	Leu	Ser	Leu	Ser	Pro	Ser	Val	Ser	Ala	Phe	Thr	Leu	Pro	Glu	Ala	50	55	60	
Trp	Arg	Ala	Ala	Gln	Gln	His	Ser	Ala	Asp	Phe	Gln	Ala	Ser	His	Tyr	65	70	75	80
Gln	Arg	Asp	Ala	Val	Arg	Ala	Arg	Gln	Gln	Gln	Ala	Lys	Ala	Ala	Phe	85	90	95	
Leu	Pro	His	Val	Ser	Ala	Asn	Ala	Ser	Tyr	Gln	Arg	Gln	Pro	Pro	Ser	100	105	110	
Ile	Ser	Ser	Thr	Arg	Glu	Thr	Gln	Gly	Trp	Ser	Val	Gln	Val	Gly	Gln	115	120	125	
Thr	Leu	Phe	Asp	Ala	Ala	Lys	Phe	Ala	Gln	Tyr	Arg	Gln	Ser	Arg	Phe	130	135	140	
Asp	Thr	Gln	Ala	Ala	Glu	Gln	Arg	Phe	Asp	Ala	Ala	Arg	Glu	Glu	Leu	145	150	155	160
Leu	Leu	Lys	Val	Ala	Glu	Ser	Tyr	Phe	Asn	Val	Leu	Leu	Ser	Arg	Asp	165	170	175	
Thr	Val	Ala	Ala	His	Ala	Ala	Glu	Lys	Glu	Ala	Tyr	Ala	Gln	Gln	Val	180	185	190	
Arg	Gln	Ala	Gln	Ala	Leu	Phe	Asn	Lys	Gly	Ala	Ala	Thr	Ala	Leu	Asp	195	200	205	
Ile	His	Glu	Ala	Lys	Ala	Gly	Tyr	Asp	Asn	Ala	Leu	Ala	Gln	Glu	Ile	210	215	220	
Ala	Val	Leu	Ala	Glu	Lys	Gln	Thr	Tyr	Glu	Asn	Gln	Leu	Asn	Asp	Tyr	225	230	235	240
Thr	Asp	Leu	Asp	Ser	Lys	Gln	Ile	Glu	Ala	Ile	Asp	Thr	Ala	Asn	Leu	245	250	255	
Leu	Ala	Arg	Tyr	Leu	Pro	Lys	Leu	Glu	Arg	Tyr	Ser	Leu	Asp	Glu	Trp	260	265	270	
Gln	Arg	Ile	Ala	Leu	Ser	Asn	Asn	His	Glu	Tyr	Arg	Met	Gln	Gln	Leu	275	280	285	
Ala	Leu	Gln	Ser	Ser	Gly	Gln	Ala	Leu	Arg	Ala	Ala	Gln	Asn	Ser	Arg	290	295	300	



Tyr Pro Thr Val Ser Ala His Val Gly Tyr Gln Asn Asn Leu Tyr Thr  
 305 310 315 320  
 Ser Ser Ala Gln Asn Asn Asp Tyr His Tyr Arg Gly Lys Gly Met Ser  
 325 330 335  
 Val Gly Val Gln Leu Asn Leu Pro Leu Tyr Thr Gly Gly Glu Leu Ser  
 340 345 350  
 Gly Lys Ile His Glu Ala Glu Ala Gln Tyr Gly Ala Ala Glu Ala Gln  
 355 360 365  
 Leu Thr Ala Thr Glu Arg His Ile Lys Leu Ala Val Arg Gln Ala Tyr  
 370 375 380  
 Thr Glu Ser Gly Ala Ala Arg Tyr Gln Ile Met Ala Gln Glu Arg Val  
 385 390 395 400  
 Leu Glu Ser Ser Arg Leu Lys Leu Lys Ser Thr Glu Thr Gly Gln Gln  
 405 410 415  
 Tyr Gly Ile Arg Asn Arg Leu Glu Val Ile Arg Ala Arg Gln Glu Val  
 420 425 430  
 Ala Gln Ala Glu Gln Lys Leu Ala Gln Ala Arg Tyr Lys Phe Met Leu  
 435 440 445  
 Ala Tyr Leu Arg Leu Val Lys Glu Ser Gly Leu Gly Leu Glu Thr Val  
 450 455 460  
 Phe Ala Glu  
 465

&lt;210&gt; 75

&lt;211&gt; 1404

&lt;212&gt; DNA

&lt;213&gt; Neisseria meningitidis

&lt;400&gt; 75

atgacattgc tcaatctaata gataatgcaa gattacggta ttccggttg cctgacactg 60  
 acgcccatt tgcaacatga actattttcg gctatgaaat cctatttttc caaatatata 120  
 ctaccggttt cactttttac ctggccacta tccctttccc catccgtttc ggcttttacg 180  
 ctgcctgaag catggcgggc ggccgagcaa cattcggctg attttcaagc gtccattac 240  
 cagcgtgatg cagtgcgcgc acggcaacaa caagccaagg ccgattcct tccccatgta 300  
 tccgccaatg ccagctacca gcgccagccg ccatcgattt ctcccaccgc cgaacacag 360  
 ggatggagcg tgcagggtgg acaaacctta tttagcgtg ccaatttgc acaataccgc 420

```

caaaagcagg tgcatacgca ggctgcagaa cagcgtttcg atgcggcacg cgaagaattg 480
ctgttgaaag ttgccgaag ttatttcaac gttttactca gccgagacac cggtgccggc 540
catgcggcgg aaaaagaggc ttatgccagc caggttaaggc aggcgcaggc ttatttcaat 600
aaagggtgctg ccaccgcgct ggatattcac gaagccaaag ccggttacga caatgccctg 660
gcccaagaaa tcgcgcgtatt ggctgagaaa caaacctatg aaaaccaggt gaacgactac 720
accgcactgg atagcaaaca aatcgaggcc atagataacc ccaacctgtt ggcacgctat 780
ctgcccgaagc tggaaagtta cagtctggat gaatggcagc gcattgcctt atccaacaat 840
catgaatacc ggatgcagca gcttgccctg caaagcagcg gacaggcgct tcgggcagca 900
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caatacgggg ccgccgaagc acagctgacc gcaaccgagc ggcacatcaa actcgccgta 1140
cgccaggctt ataccgaaag cgggtgcggcg cgttaccaaa tcatggcgca agaacggggt 1200
ttgaaagaca gccgtttgaa actgaaatcg accgaaaccg gccacaataa cggcatccgc 1260
aaccggctgg aagtaatacg ggcgcggcag gaagtcgccc aagcagaaca gaaactggct 1320
caagcacggg ataaattcat gctggcttat ttgcgcttgg tgaagagagc cggggttagg 1380
ttggaacggg tatttgcgga ataa 1404

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&lt;210&gt; 76

&lt;211&gt; 467

&lt;212&gt; PRT

&lt;213&gt; Neisseria meningitidis

&lt;400&gt; 76

```

Met Thr Leu Leu Asn Leu Met Ile Met Gln Asp Tyr Gly Ile Ser Val
  1                      5              10              15

```

```

Cys Leu Thr Leu Thr Pro Tyr Leu Gln His Glu Leu Phe Ser Ala Met
                20              25              30

```

```

Lys Ser Tyr Phe Ser Lys Tyr Ile Leu Pro Val Ser Leu Phe Thr Leu
  35                      40              45

```

```

Pro Leu Ser Leu Ser Pro Ser Val Ser Ala Phe Thr Leu Pro Glu Ala
  50                      55              60

```

```

Trp Arg Ala Ala Gln Gln His Ser Ala Asp Phe Gln Ala Ser His Tyr
  65                      70              75              80

```

```

Gln Arg Asp Ala Val Arg Ala Arg Gln Gln Gln Ala Lys Ala Ala Phe
                85              90              95

```

```

Leu Pro His Val Ser Ala Asn Ala Ser Tyr Gln Arg Gln Pro Pro Ser
                100              105              110

```

```

Ile Ser Ser Thr Arg Glu Thr Gln Gly Trp Ser Val Gln Val Gly Gln
  115                      120              125

```

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Thr Leu Phe Asp Ala Ala Lys Phe Ala Gln Tyr Arg Gln Ser Arg Phe  
130 135 140

Asp Thr Gln Ala Ala Glu Gln Arg Phe Asp Ala Ala Arg Glu Glu Leu  
145 150 155 160

Leu Leu Lys Val Ala Glu Ser Tyr Phe Asn Val Leu Leu Ser Arg Asp  
165 170 175

Thr Val Ala Ala His Ala Ala Glu Lys Glu Ala Tyr Ala Gln Gln Val  
180 185 190

Arg Gln Ala Gln Ala Leu Phe Asn Lys Gly Ala Ala Thr Ala Leu Asp  
195 200 205

Ile His Glu Ala Lys Ala Gly Tyr Asp Asn Ala Leu Ala Gln Glu Ile  
210 215 220

Ala Val Leu Ala Glu Lys Gln Thr Tyr Glu Asn Gln Leu Asn Asp Tyr  
225 230 235 240

Thr Asp Leu Asp Ser Lys Gln Ile Glu Ala Ile Asp Thr Ala Asn Leu  
245 250 255

Leu Ala Arg Tyr Leu Pro Lys Leu Glu Arg Tyr Ser Leu Asp Glu Trp  
260 265 270

Gln Arg Ile Ala Leu Ser Asn Asn His Glu Tyr Arg Met Gln Gln Leu  
275 280 285

Ala Leu Gln Ser Ser Gly Gln Ala Leu Arg Ala Ala Gln Asn Ser Arg  
290 295 300

Tyr Pro Thr Val Ser Ala His Val Gly Tyr Gln Asn Asn Leu Tyr Thr  
305 310 315 320

Ser Ser Ala Gln Asn Asn Asp Tyr His Tyr Arg Gly Lys Gly Met Ser  
325 330 335

Val Gly Val Gln Leu Asn Leu Pro Leu Tyr Thr Gly Gly Glu Leu Ser  
340 345 350

Gly Lys Ile His Glu Ala Glu Ala Gln Tyr Gly Ala Ala Glu Ala Gln  
355 360 365

Leu Thr Ala Thr Glu Arg His Ile Lys Leu Ala Val Arg Gln Ala Tyr  
370 375 380

Thr Glu Ser Gly Ala Ala Arg Tyr Gln Ile Met Ala Gln Glu Arg Val  
385 390 395 400

Leu Glu Ser Ser Arg Leu Lys Leu Lys Ser Thr Glu Thr Gly Gln Gln  
405 410 415

Tyr Gly Ile Arg Asn Arg Leu Glu Val Ile Arg Ala Arg Gln Glu Val  
420 425 430

Ala Gln Ala Glu Gln Lys Leu Ala Gln Ala Arg Tyr Lys Phe Met Leu  
435 440 445

Ala Tyr Leu Arg Leu Val Lys Glu Ser Gly Leu Gly Leu Glu Thr Val  
450 455 460

Phe Ala Glu  
465

<210> 77

<211> 1404

<212> DNA

<213> Neisseria meningitidis

<400> 77

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ctacccgttt cactttttac cttgccaacta tccctttccc catccgtttc ggctttttacg 180  
ctgcctgaag catggcgggc ggcgcagcaa cattcggctg attttcaagc gtcccattac 240  
cagcgtgatg cagtgcgcgc acgcgaacaa caagccaagg ccgcattcct tccccatgta 300  
tccgcacaatg ccagctacca gcgcagccgc ccattcgattt cttccaccgc cgaacacacg 360  
ggatggagcg tgcaggtggg acaaacctta ttgacgctg ccaaaattgc acaattaccg 420  
caaagcaggt tgcatacgca ggctgcagaa cagcgttttc atgcggcagc cgaagaattg 480  
ctgttgaaag ttgcccgaag ttattttcaac gttttactca gccgagacac cgttgccgcc 540  
catgcggcgg aaaaagaggc ttatgccagc caggtaaggc aggcgcaggc tttattcaat 600  
aaaggtgctg ccaccgcgct ggatattcac gaagccaagg ccggttacga caatgccctg 660  
gcccaagaaa tcgcgctatt ggctgagaaa caaacctatg aaaaccagtt gaacgactac 720  
accgacctgg atagcaacaa aatcgaggcc atagataccg ccaacctgtt ggcacgctat 780  
ctgcccacagc tggaaactga cagtctggat gaatggcagc gcattgcctt atccaacaat 840  
catgaatacc ggatgcagca gcttgccttg caaagcagcg gacagcgctt tcgggcagca 900  
cagaacagcc gctatccac cgtttctgcc catgtcggct atcagaataa cctctacact 960  
tcatctgcgc agaataatga ctaccactat cggggcaaa ggtatgagcgt cggcgtacag 1020  
ttgaatttgc cgtttttatc cggcggagaa ttgtcgggca aaatccatga agccgaagcg 1080  
caatacgggg ccgcggaagc acagctgacc gcaaccagc ggcacatcaa actcgcctga 1140  
cgccaggctt ataccgaaa cggtgcggcg cgttaccaaa tcatggcgca agaaccgggt 1200  
ttggaaagca gccgtttgaa actgaaatcg accgaaaccg gccaaacaata cggcatccgc 1260  
aaccggcttg aagtaatacg ggcgcggcag gaagtcgccc aagcagaaca gaaactggct 1320  
caagcacggt ataaattcat gctggcttat ttgcgcttg tgaaagagag cgggttaggg 1380

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ttgqaaacqg tatttgcgga ataa

1404

<210> 78

<211> 467

&lt;212&gt; PRT

<213> *Neisseria meningitidis*

&lt;400&gt; 78

Met Thr Leu Leu Asn Leu Met Ile Met Gln Asp Tyr Gly Ile Ser Val  
1 5 10 15

Cys Leu Thr Leu Thr Pro Tyr Leu Gln His Glu Leu Phe Ser Ala Met  
20 25 30

Lys Ser Tyr Phe Ser Lys Tyr Ile Leu Pro Val Ser Leu Phe Thr Leu  
35 40 45

Pro Leu Ser Leu Ser Pro Ser Val Ser Ala Phe Thr Leu Pro Glu Ala  
50 55 60

Trp	Arg	Ala	Ala	Gln	Gln	His	Ser	Ala	Asp	Phe	Gln	Ala	Ser	His	Tyr
65					70					75					80

Gln Arg Asp Ala Val Arg Ala Arg Gln Gln Gln Ala Lys Ala Ala Phe  
85 90 95

Leu Pro His Val Ser Ala Asn Ala Ser Tyr Gln Arg Gln Pro Pro Ser  
100 105 110

Ile Ser Ser Thr Arg Glu Thr Gln Gly Trp Ser Val Gln Val Gly Gln  
115 120 125

Thr Leu Phe Asp Ala Ala Lys Phe Ala Gln Tyr Arg Gln Ser Arg Phe  
130 135 140

Asp Thr Gln Ala Ala Glu Gln Arg Phe Asp Ala Ala Arg Glu Glu Leu  
145 150 155 160

Leu Leu Lys Val Ala Glu Ser Tyr Phe Asn Val Leu Leu Ser Arg Asp  
165 170 175

Thr Val Ala Ala His Ala Ala Glu Lys Glu Ala Tyr Ala Gln Gln Val  
180 185 190

Arg Gln Ala Gln Ala Leu Phe Asn Lys Gly Ala Ala Thr Ala Leu Asp  
195 200 205

Ile His Glu Ala Lys Ala Gly Tyr Asp Asn Ala Leu Ala Gln Glu Ile

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210 215 220

Ala Val Leu Ala Glu Lys Gln Thr Tyr Glu Asn Gln Leu Asn Asp Tyr  
225 230 235 240

Thr Asp Leu Asp Ser Lys Gln Ile Glu Ala Ile Asp Thr Ala Asn Leu  
245 250 255

Leu Ala Arg Tyr Leu Pro Lys Leu Glu Arg Tyr Ser Leu Asp Glu Trp  
260 265 270

Gln Arg Ile Ala Leu Ser Asn Asn His Glu Tyr Arg Met Gln Gln Leu  
275 280 285

Ala Leu Gln Ser Ser Gly Gln Ala Leu Arg Ala Ala Gln Asn Ser Arg  
290 295 300

Tyr Pro Thr Val Ser Ala His Val Gly Tyr Gln Asn Asn Leu Tyr Thr  
305 310 315 320

Ser Ser Ala Gln Asn Asn Asp Tyr His Tyr Arg Gly Lys Gly Met Ser  
325 330 335

Val Gly Val Gln Leu Asn Leu Pro Leu Tyr Thr Gly Gly Glu Leu Ser  
340 345 350

Gly Lys Ile His Glu Ala Glu Ala Gln Tyr Gly Ala Ala Glu Ala Gln  
355 360 365

Leu Thr Ala Thr Glu Arg His Ile Lys Leu Ala Val Arg Gln Ala Tyr  
370 375 380

Thr Glu Ser Gly Ala Ala Arg Tyr Gln Ile Met Ala Gln Glu Arg Val  
385 390 395 400

Leu Glu Ser Ser Arg Leu Lys Leu Lys Ser Thr Glu Thr Gly Gln Gln  
405 410 415

Tyr Gly Ile Arg Asn Arg Leu Glu Val Ile Arg Ala Arg Gln Glu Val  
420 425 430

Ala Gln Ala Glu Gln Lys Leu Ala Gln Ala Arg Tyr Lys Phe Met Leu  
435 440 445

Ala Tyr Leu Arg Leu Val Lys Glu Ser Gly Leu Gly Leu Glu Thr Val  
450 455 460

Phe Ala Glu

465

&lt;210&gt; 79

&lt;211&gt; 1404

&lt;212&gt; DNA

<213> *Neisseria meningitidis*

&lt;400&gt; 79

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ctaccgggtt cacttttttc cttgccacta tccctttccc catccgtttc ggctttttacg 180
ctgcctgaag catggcgggc ggcgagcaa cattcggctg attttcaagc gtcccattac 240
cagcgtgatg cagtgcgcgc acggcaacaa caagccaagg ccgcattcct tccccatgta 300
tccgccaatg ccagctacca ggcgcagccg ccctcgattt cttccaccgc cgaacacag 360
ggatggagcg tgcaggtggg acaaacctta ttgacgctg ccaaatgtgc acaataccgc 420
caaagcaggt tgcatacgca ggctgcagaa cagcgtttcg atgcggcagc cgaagaattg 480
ctgttgaaag ttgccgaaa ttatttcaac gttttactca gccgagacac cgttgccgcc 540
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aaaggtgctg ccaccgcgct ggatattcac gaagccaaag ccggttacga caatgccctg 660
gcccaagaaa tcgcgttatt ggctgagaaa caaacctatg aaaaccagtt gaacgactac 720
accgacctgg atagcaaaaca aatcgaggcc atagataccg ccaacctgtt ggcacgctat 780
ctgcccaagc tggaacgtta cagtctggat gaattggcagc gcattgcctt atccaacaat 840
catgaatacc ggatgcagca gcttgccttg caaagcagcg gacagggcgt tcggggcagca 900
cagaacagcc gctatccac cgtttctgcc catgtcggct atcagaataa cctctacact 960
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ttgaaagcga gccgtttgaa actgaaatcg accgaaaccg gccacaataa cggcatccgc 1260
aaccggcttg aagtaatacg ggcgcggcag gaagtgcgcc aagcagaaca gaaactggct 1320
caagcacggt ataaattcat gctggcttat ttgcgcttgg tgaagagag cgggttaggg 1380
ttggaacagg tatttgcgga ataa 1404

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&lt;210&gt; 80

&lt;211&gt; 467

&lt;212&gt; PRT

<213> *Neisseria meningitidis*

&lt;400&gt; 80

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Met Thr Leu Leu Asn Leu Met Ile Met Gln Asp Tyr Gly Ile Ser Val
      1              5              10             15

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Cys Leu Thr Leu Thr Pro Tyr Leu Gln His Glu Leu Phe Ser Ala Met
      20              25              30

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Lys Ser Tyr Phe Ser Lys Tyr Ile Leu Pro Val Ser Leu Phe Thr Leu
      35              40              45

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Pro Leu Ser Leu Ser Pro Ser Val Ser Ala Phe Thr Leu Pro Glu Ala  
50 55 60

Trp Arg Ala Ala Gln Gln His Ser Ala Asp Phe Gln Ala Ser His Tyr  
65 70 75 80

Gln Arg Asp Ala Val Arg Ala Arg Gln Gln Gln Ala Lys Ala Ala Phe  
85 90 95

Leu Pro His Val Ser Ala Asn Ala Ser Tyr Gln Arg Gln Pro Pro Ser  
100 105 110

Ile Ser Ser Thr Arg Glu Thr Gln Gly Trp Ser Val Gln Val Gly Gln  
115 120 125

Thr Leu Phe Asp Ala Ala Lys Phe Ala Gln Tyr Arg Gln Ser Arg Phe  
130 135 140

Asp Thr Gln Ala Ala Glu Gln Arg Phe Asp Ala Ala Arg Glu Glu Leu  
145 150 155 160

Leu Leu Lys Val Ala Glu Ser Tyr Phe Asn Val Leu Leu Ser Arg Asp  
165 170 175

Thr Val Ala Ala His Ala Ala Glu Lys Glu Ala Tyr Ala Gln Gln Val  
180 185 190

Arg Gln Ala Gln Ala Leu Phe Asn Lys Gly Ala Ala Thr Ala Leu Asp  
195 200 205

Ile His Glu Ala Lys Ala Gly Tyr Asp Asn Ala Leu Ala Gln Glu Ile  
210 215 220

Ala Val Leu Ala Glu Lys Gln Thr Tyr Glu Asn Gln Leu Asn Asp Tyr  
225 230 235 240

Thr Asp Leu Asp Ser Lys Gln Ile Glu Ala Ile Asp Thr Ala Asn Leu  
245 250 255

Leu Ala Arg Tyr Leu Pro Lys Leu Glu Arg Tyr Ser Leu Asp Glu Trp  
260 265 270

Gln Arg Ile Ala Leu Ser Asn Asn His Glu Tyr Arg Met Gln Gln Leu  
275 280 285

Ala Leu Gln Ser Ser Gly Gln Ala Leu Arg Ala Ala Gln Asn Ser Arg  
290 295 300



Tyr Pro Thr Val Ser Ala His Val Gly Tyr Gln Asn Asn Leu Tyr Thr  
305 310 315 320

Ser Ser Ala Gln Asn Asn Asp Tyr His Tyr Arg Gly Lys Gly Met Ser  
325 330 335

Val Gly Val Gln Leu Asn Leu Pro Leu Tyr Thr Gly Gly Glu Leu Ser  
340 345 350

Gly Lys Ile His Glu Ala Glu Ala Gln Tyr Gly Ala Ala Glu Ala Gln  
355 360 365

Leu Thr Ala Thr Glu Arg His Ile Lys Leu Ala Val Arg Gln Ala Tyr  
370 375 380

Thr Glu Ser Gly Ala Ala Arg Tyr Gln Ile Met Ala Gln Glu Arg Val  
385 390 395 400

Leu Glu Ser Ser Arg Leu Lys Leu Lys Ser Thr Glu Thr Gly Gln Gln  
405 410 415

Tyr Gly Ile Arg Asn Arg Leu Glu Val Ile Arg Ala Arg Gln Glu Val  
420 425 430

Ala Gln Ala Glu Gln Lys Leu Ala Gln Ala Arg Tyr Lys Phe Met Leu  
435 440 445

Ala Tyr Leu Arg Leu Val Lys Glu Ser Gly Leu Gly Leu Glu Thr Val  
450 455 460

Phe Ala Glu  
465

<210> 81

<211> 1404

<212> DNA

<213> Neisseria meningitidis

<400> 81

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ctaccocgttt cactttttac cttgccacta tccctttccc catccgtttc ggctttttacg 180  
ctgcctgaag catggcgggc ggcgcagcaa cattcggctg attttcaagc gtcccattac 240  
cagcgtgatg cagtgcgcgc acggcaacaa caagccaagg ccgcattcct tcccattga 300  
tcgcacaatg ccagctaacca gcgcagccg ccattcgattt cttccaccog cgaacacag 360

ggatggagcg tgcaggtggg acaaacctta ttgacgctg ccaaatttgc acaataccgc 420  
 caaagcaggt tcgatacgca ggctgcagaa cagcggttgc atcgggcagc cgaagaattg 480  
 ctgttgaaaag ttgccgaaaag ttatttcaac gttttactca gccgagacac cgttgccgcc 540  
 catgcggcgg aaaaagagcg ttatgcccgag caggttaaggc aggcgcagcg ttatttcaat 600  
 aaaggtgctg ccaccgcgct ggatattcac gaagccaaaag ccggttacga caatgccctg 660  
 gcccaagaaa tcgccgtatt ggctgagaaa caaacctatg aaaaccagtt gaacgactac 720  
 accgacctgg atagcaaaag aatcgaggcc atagataccg ccaacctgtt gccacgctat 780  
 ctgcccgaagc tggaaagtta cagtctggat gaatggcagc gcattgcctt atccaacaat 840  
 catgaatacc ggatgcagca gcttgcctg caaagcagcg gacaggcgtt tcgggcagca 900  
 cagaacagcc gctatccac cgtttctgcc catgtcggct atcagaataa cctctacact 960  
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 caatacgggg ccgccgaagc acagctgacc gcaaccgagc gccacatcaa actcgccgta 1140  
 cgccaagctt ataccgaaaag cgggtcggcg cgttaccaaa tcatggcgca agaacgggtt 1200  
 ttggaagaca gccgtttgaa actgaaatcg accgaaaccg gccacaataa cggcatccgc 1260  
 aaccggctgg aagtaatacg ggcgcggcag gaagtcgccc aagcagaaca gaaactggct 1320  
 caagcacggt ataaattcat gctggttat ttgcgcttg tgaagagagc cgggttaggg 1380  
 ttggaacggg tatttgcgga ataa 1404

&lt;210&gt; 82

&lt;211&gt; 467

&lt;212&gt; PRT

&lt;213&gt; Neisseria meningitidis

&lt;400&gt; 82

Met Thr Leu Leu Asn Leu Met Ile Met Gln Asp Tyr Gly Ile Ser Val  
 1 5 10 15

Cys Leu Thr Leu Thr Pro Tyr Leu Gln His Glu Leu Phe Ser Ala Met  
 20 25 30

Lys Ser Tyr Phe Ser Lys Tyr Ile Leu Pro Val Ser Leu Phe Thr Leu  
 35 40 45

Pro Leu Ser Leu Ser Pro Ser Val Ser Ala Phe Thr Leu Pro Glu Ala  
 50 55 60

Trp Arg Ala Ala Gln Gln His Ser Ala Asp Phe Gln Ala Ser His Tyr  
 65 70 75 80

Gln Arg Asp Ala Val Arg Ala Arg Gln Gln Gln Ala Lys Ala Ala Phe  
 85 90 95

Leu Pro His Val Ser Ala Asn Ala Ser Tyr Gln Arg Gln Pro Pro Ser  
 100 105 110

Ile Ser Ser Thr Arg Glu Thr Gln Gly Trp Ser Val Gln Val Gly Gln  
 115 120 125

Thr Leu Phe Asp Ala Ala Lys Phe Ala Gln Tyr Arg Gln Ser Arg Phe  
130 135 140

Asp Thr Gln Ala Ala Glu Gln Arg Phe Asp Ala Ala Arg Glu Glu Leu  
145 150 155 160

Leu Leu Lys Val Ala Glu Ser Tyr Phe Asn Val Leu Leu Ser Arg Asp  
165 170 175

Thr Val Ala Ala His Ala Ala Glu Lys Glu Ala Tyr Ala Gln Gln Val  
180 185 190

Arg Gln Ala Gln Ala Leu Phe Asn Lys Gly Ala Ala Thr Ala Leu Asp  
195 200 205

Ile His Glu Ala Lys Ala Gly Tyr Asp Asn Ala Leu Ala Gln Glu Ile  
210 215 220

Ala Val Leu Ala Glu Lys Gln Thr Tyr Glu Asn Gln Leu Asn Asp Tyr  
225 230 235 240

Thr Asp Leu Asp Ser Lys Gln Ile Glu Ala Ile Asp Thr Ala Asn Leu  
245 250 255

Leu Ala Arg Tyr Leu Pro Lys Leu Glu Arg Tyr Ser Leu Asp Glu Trp  
260 265 270

Gln Arg Ile Ala Leu Ser Asn Asn His Glu Tyr Arg Met Gln Gln Leu  
275 280 285

Ala Leu Gln Ser Ser Gly Gln Ala Leu Arg Ala Ala Gln Asn Ser Arg  
290 295 300

Tyr Pro Thr Val Ser Ala His Val Gly Tyr Gln Asn Asn Leu Tyr Thr  
305 310 315 320

Ser Ser Ala Gln Asn Asn Asp Tyr His Tyr Arg Gly Lys Gly Met Ser  
325 330 335

Val Gly Val Gln Leu Asn Leu Pro Leu Tyr Thr Gly Gly Glu Leu Ser  
340 345 350

Gly Lys Ile His Glu Ala Glu Ala Gln Tyr Gly Ala Ala Glu Ala Gln  
355 360 365

Leu Thr Ala Thr Glu Arg His Ile Lys Leu Ala Val Arg Gln Ala Tyr  
370 375 380

Thr Glu Ser Gly Ala Ala Arg Tyr Gln Ile Met Ala Gln Glu Arg Val  
 385 390 395 400

Leu Glu Ser Ser Arg Leu Lys Leu Lys Ser Thr Glu Thr Gly Gln Gln  
 405 410 415

Tyr Gly Ile Arg Asn Arg Leu Glu Val Ile Arg Ala Arg Gln Glu Val  
 420 425 430

Ala Gln Ala Glu Gln Lys Leu Ala Gln Ala Arg Tyr Lys Phe Met Leu  
 435 440 445

Ala Tyr Leu Arg Leu Val Lys Glu Ser Gly Leu Gly Leu Glu Thr Val  
 450 455 460

Phe Ala Glu  
 465

<210> 83

<211> 1404

<212> DNA

<213> *Neisseria meningitidis*

<400> 83

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 ctaccggttt cactttttac cttgccaacta tccctttccc catccgtttc ggctttttacg 180  
 ctgacctgaag catggcggggc ggcgcagcaa cattcggtcg attttcaagc gtccattac 240  
 cagcgtgatg cagtgccgcgc acggcaacaa caagccaagg ccgcattcct tccccatgta 300  
 tccgccaatg ccagctacca gcgccagccg ccatcgattt cttccaccgc cgaacacag 360  
 ggatggagcg tgcaggtggg acaaacctta ttgacgctg ccaaatattg acaataccgc 420  
 caaagcaggt tcgatacgca ggtgcagaa cagcggtttg atcgccgacg cgaagaattg 480  
 ctgttgaaaag ttgccgaaa ttatttcaac gttttactca gccgagacac cgttgcgcgc 540  
 catgcggcgg aaaaagaggc ttatgccagc caggttaaggc aggcgcaggc ttatttcaat 600  
 aaaggtgctg ccaccgcgct ggatattcac gaagccaaa ccggttacga caatgcctg 660  
 gcccaagaaa tcgccgtatt ggctgagaaa caaacctatg aaacacagtt gaacgactac 720  
 accgacctgg atagcaaaac aatcgaggcc atagataccg ccaacctgtt ggcacgctat 780  
 ctgcccgaagc ttgaacgtta cagtctggat gaatggcagc gcattgcctt atccaacaat 840  
 catgaatacc ggatgcagca gcttgccctg caagcagcg gcagcgctc tcgggcagca 900  
 cagaacagcc gctatccac cgtttctgcc catgtcggct atcagaataa cctctacact 960  
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 caatcagggg ccgcccgaagc acagctgacc gcaaccgagc ggcacatcaa actcgcgcta 1140  
 cgccaggctt ataccgaaa cggtgcggcg cgttaccaaa tcatggcgca agaaccgggt 1200  
 ttggaaagca gccgtttgaa actgaaatcg accgaaaccg gccacaata cggcatccgc 1260  
 aaccggctgg aagtaatacg ggcgcggcag gaagtcgccc aagcagaaca gaaactggct 1320

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caagcacggt ataaattcat gctggcttat ttgcgcttgg tgaagagag cggttaggg 1380  
ttggaaacgg tatttgcgga ataa 1404

<210> 84

<211> 467

<212> PRT

<213> Neisseria meningitidis

<400> 84

Met Thr Leu Leu Asn Leu Met Ile Met Gln Asp Tyr Gly Ile Ser Val  
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Cys Leu Thr Leu Thr Pro Tyr Leu Gln His Glu Leu Phe Ser Ala Met  
20 25 30

Lys Ser Tyr Phe Ser Lys Tyr Ile Leu Pro Val Ser Leu Phe Thr Leu  
35 40 45

Pro Leu Ser Leu Ser Pro Ser Val Ser Ala Phe Thr Leu Pro Glu Ala  
50 55 60

Trp Arg Ala Ala Gln Gln His Ser Ala Asp Phe Gln Ala Ser His Tyr  
65 70 75 80

Gln Arg Asp Ala Val Arg Ala Arg Gln Gln Gln Ala Lys Ala Ala Phe  
85 90 95

Leu Pro His Val Ser Ala Asn Ala Ser Tyr Gln Arg Gln Pro Pro Ser  
100 105 110

Ile Ser Ser Thr Arg Glu Thr Gln Gly Trp Ser Val Gln Val Gly Gln  
115 120 125

Thr Leu Phe Asp Ala Ala Lys Phe Ala Gln Tyr Arg Gln Ser Arg Phe  
130 135 140

Asp Thr Gln Ala Ala Glu Gln Arg Phe Asp Ala Ala Arg Glu Glu Leu  
145 150 155 160

Leu Leu Lys Val Ala Glu Ser Tyr Phe Asn Val Leu Leu Ser Arg Asp  
165 170 175

Thr Val Ala Ala His Ala Ala Glu Lys Glu Ala Tyr Ala Gln Gln Val  
180 185 190

Arg Gln Ala Gln Ala Leu Phe Asn Lys Gly Ala Ala Thr Ala Leu Asp  
195 200 205

Ile His Glu Ala Lys Ala Gly Tyr Asp Asn Ala Leu Ala Gln Glu Ile  
 210 215 220

Ala Val Leu Ala Glu Lys Gln Thr Tyr Glu Asn Gln Leu Asn Asp Tyr  
 225 230 235 240

Thr Asp Leu Asp Ser Lys Gln Ile Glu Ala Ile Asp Thr Ala Asn Leu  
 245 250 255

Leu Ala Arg Tyr Leu Pro Lys Leu Glu Arg Tyr Ser Leu Asp Glu Trp  
 260 265 270

Gln Arg Ile Ala Leu Ser Asn Asn His Glu Tyr Arg Met Gln Gln Leu  
 275 280 285

Ala Leu Gln Ser Ser Gly Gln Ala Leu Arg Ala Ala Gln Asn Ser Arg  
 290 295 300

Tyr Pro Thr Val Ser Ala His Val Gly Tyr Gln Asn Asn Leu Tyr Thr  
 305 310 315 320

Ser Ser Ala Gln Asn Asn Asp Tyr His Tyr Arg Gly Lys Gly Met Ser  
 325 330 335

Val Gly Val Gln Leu Asn Leu Pro Leu Tyr Thr Gly Gly Glu Leu Ser  
 340 345 350

Gly Lys Ile His Glu Ala Glu Ala Gln Tyr Gly Ala Ala Glu Ala Gln  
 355 360 365

Leu Thr Ala Thr Glu Arg His Ile Lys Leu Ala Val Arg Gln Ala Tyr  
 370 375 380

Thr Glu Ser Gly Ala Ala Arg Tyr Gln Ile Met Ala Gln Glu Arg Val  
 385 390 395 400

Leu Glu Ser Ser Arg Leu Lys Leu Lys Ser Thr Glu Thr Gly Gln Gln  
 405 410 415

Tyr Gly Ile Arg Asn Arg Leu Glu Val Ile Arg Ala Arg Gln Glu Val  
 420 425 430

Ala Gln Ala Glu Gln Lys Leu Ala Gln Ala Arg Tyr Lys Phe Met Leu  
 435 440 445

Ala Tyr Leu Arg Leu Val Lys Glu Ser Gly Leu Gly Leu Glu Thr Val  
 450 455 460

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Phe Ala Glu  
465

<210> 85

<211> 1404

<212> DNA

<213> Neisseria meningitidis

<400> 85

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ctacccgctt cacttttttac cttgccacta tccctttccc catccgcttc ggctttttacg 180  
ctgcctgaag catggcgggc gccgcagcaa cattcggctg attttcaagc gtcccattac 240  
cagcgtgatg cagtgcgcgc acggcaacaa caagccaagg ccgcattcct tccccatgta 300  
tcgcacaatg ccagctacca gcgccagccg ccctcgattt cttccacccc cgaacacacag 360  
ggatggagcg tgcaggtggg acaaacctta tttgacgctg ccaaatattgc acaataccgc 420  
caaaagcaggt tcgatacgca ggctgcagaa cagcgtttcg atgcggcacg cgaagaattg 480  
ctgttgaaaag ttgccgaaaag ttatttcaac gttttactca gccgagacac cgttgccgcc 540  
catgcggcgg aaaaagaggc ttatgccagc caggtaaagg aggcgcagggc tttattcaat 600  
aaaggtgctg ccaccgcgct ggatattcac gaagccaagg ccggttacga caatgccctg 660  
gcccaagaaa tcgctgattt ggctgagaaa caaacctatg aaaaccagtt gaacgactac 720  
accgacctgg atagcaaaaca aatcgaggcc atagataccg ccaacctgtt ggcacgctat 780  
ctgcccacgc tggaaacgtta cagtctggat gaatggcagc gcattgcctt atccaacaat 840  
catgaatacc ggatgcagca gcttgccctg caaagcagcg gacagcgct tcgggcagca 900  
cagaacagcc gctatccac cgtttctgcc catgtcggct atcagaataa cctctacact 960  
tcactctgcg agaataatga ctaccactat cggggcaagg ggatgagcgt cggcgtagac 1020  
ttgaatttgc cgctttatgc cggcggaaga ttgtcgggca aaatccatga agccgaagcg 1080  
caatacgggg ccgccgaagc acagctgacc gcaaccgagc ggcacatcaa actcgcctga 1140  
cgccaggctt ataccgaaag cgttgccggc cgttaccaaa tcattggcgcga agaacggggt 1200  
ttggaaagca gccgtttgaa actgaaatcg accgaaaccg gccacaataa cggcatccgc 1260  
aaccggctgg aagtaatacg ggcgcggcag gaagtgcgcc aagcagaaca gaaactggct 1320  
caagcacggt ataaattcat gctgcttat ttgcgcttgc tgaagagag cgggttaggg 1380  
ttggaacggg tatttgccga ataa 1404

<210> 86

<211> 467

<212> PRT

<213> Neisseria meningitidis

<400> 86

Met Thr Leu Leu Asn Leu Met Ile Met Gln Asp Tyr Gly Ile Ser Val  
1 5 10 15

Cys Leu Thr Leu Thr Pro Tyr Leu Gln His Glu Leu Phe Ser Ala Met  
20 25 30

Lys Ser Tyr Phe Ser Lys Tyr Ile Leu Pro Val Ser Leu Phe Thr Leu

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35	40	45
Pro Leu Ser Leu Ser Pro Ser Val Ser Ala Phe Thr Leu Pro Glu Ala		
50	55	60
Trp Arg Ala Ala Gln Gln His Ser Ala Asp Phe Gln Ala Ser His Tyr		
65	70	75 80
Gln Arg Asp Ala Val Arg Ala Arg Gln Gln Gln Ala Lys Ala Ala Phe		
85	90	95
Leu Pro His Val Ser Ala Asn Ala Ser Tyr Gln Arg Gln Pro Pro Ser		
100	105	110
Ile Ser Ser Thr Arg Glu Thr Gln Gly Trp Ser Val Gln Val Gly Gln		
115	120	125
Thr Leu Phe Asp Ala Ala Lys Phe Ala Gln Tyr Arg Gln Ser Arg Phe		
130	135	140
Asp Thr Gln Ala Ala Glu Gln Arg Phe Asp Ala Ala Arg Glu Glu Leu		
145	150	155 160
Leu Leu Lys Val Ala Glu Ser Tyr Phe Asn Val Leu Leu Ser Arg Asp		
165	170	175
Thr Val Ala Ala His Ala Ala Glu Lys Glu Ala Tyr Ala Gln Gln Val		
180	185	190
Arg Gln Ala Gln Ala Leu Phe Asn Lys Gly Ala Ala Thr Ala Leu Asp		
195	200	205
Ile His Glu Ala Lys Ala Gly Tyr Asp Asn Ala Leu Ala Gln Glu Ile		
210	215	220
Ala Val Leu Ala Glu Lys Gln Thr Tyr Glu Asn Gln Leu Asn Asp Tyr		
225	230	235 240
Thr Asp Leu Asp Ser Lys Gln Ile Glu Ala Ile Asp Thr Ala Asn Leu		
245	250	255
Leu Ala Arg Tyr Leu Pro Lys Leu Glu Arg Tyr Ser Leu Asp Glu Trp		
260	265	270
Gln Arg Ile Ala Leu Ser Asn Asn His Glu Tyr Arg Met Gln Gln Leu		
275	280	285
Ala Leu Gln Ser Ser Gly Gln Ala Leu Arg Ala Ala Gln Asn Ser Arg		



290

295

300

Tyr Pro Thr Val Ser Ala His Val Gly Tyr Gln Asn Asn Leu Tyr Thr  
 305 310 315 320

Ser Ser Ala Gln Asn Asn Asp Tyr His Tyr Arg Gly Lys Gly Met Ser  
 325 330 335

Val Gly Val Gln Leu Asn Leu Pro Leu Tyr Thr Gly Gly Glu Leu Ser  
 340 345 350

Gly Lys Ile His Glu Ala Glu Ala Gln Tyr Gly Ala Ala Glu Ala Gln  
 355 360 365

Leu Thr Ala Thr Glu Arg His Ile Lys Leu Ala Val Arg Gln Ala Tyr  
 370 375 380

Thr Glu Ser Gly Ala Ala Arg Tyr Gln Ile Met Ala Gln Glu Arg Val  
 385 390 395 400

Leu Glu Ser Ser Arg Leu Lys Leu Lys Ser Thr Glu Thr Gly Gln Gln  
 405 410 415

Tyr Gly Ile Arg Asn Arg Leu Glu Val Ile Arg Ala Arg Gln Glu Val  
 420 425 430

Ala Gln Ala Glu Gln Lys Leu Ala Gln Ala Arg Tyr Lys Phe Met Leu  
 435 440 445

Ala Tyr Leu Arg Leu Val Lys Glu Ser Gly Leu Gly Leu Glu Thr Val  
 450 455 460

Phe Ala Glu  
 465

&lt;210&gt; 87

&lt;211&gt; 1404

&lt;212&gt; DNA

&lt;213&gt; Neisseria meningitidis

&lt;400&gt; 87

atgacattgc tcaatcctaat gataatgcaa gattacggta tttccggttg cctgacactg 60  
 acgcccattt tgcaacatga actattttcg gctatgaaat cctatttttc caaatatattc 120  
 ctaccggttt cactttttac ctggccacta tccctttccc cctccgtttc ggctttttacg 180  
 ctgacctgaag catggcgggc ggcgcagcaa cattcggctg attttcaagc gtcccatctac 240  
 cagcgtgatg cagtgcgcgc acggcaacaa caagccaagg ccgcattcct tccccatgta 300  
 tccgccaatg ccagctacca gcgcccagcc ccatcgattt ctccaccggc cgaacacag 360

```

ggatgggagcg tgcagggtggg acaaacctta ttgacgctg ccaaatttgc acaataccgc 420
caaagcaggt tcgatacgca ggctgcagaa cagcgtttcg atcgggcagc cgaagaattg 480
ctgttgaaag ttgcccgaag ttatttcaac gttttactca gccgagacac cgttgcgcc 540
catgcgcgcg aaaaagaggg ttatgcccg caggtaaagg aggcgcagggc ttatttcaat 600
aaaggtgctg ccaccgcgct ggatattcac gaagccaaag ccggttagca caatgccctg 660
gcccaagaaa tcgccgtatt ggctgagaaa caaacctatg aaaaccagtt gaacgactac 720
accgacctgg atagcaaaaca aatcgaggcc atagatacgg ccaacctgtt ggcacgctat 780
ctgcccgaagc tggaacgtta cagtctggat gaatggcagc gcattgcctt atccaacaat 840
catgaatacc ggatgcagca gcttgcctg caaagcagcg gacaggcgct tcgggcagca 900
cagaacagcc gctatccac cggtttctgccc catgtcggct atcagaataa cctctacact 960
tcattctgccc agaataatga ctaccactat cggggcaaa ggaatgagcg cgcgctacag 1020
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caatacgggg ccgccgaagc acagctgacc gcaaccgagc ggcacatcaa actcgccgta 1140
cgccaggctt ataccgaaag cggtgcggcg cgttacaaaa tcattggcgca agaacggggt 1200
ttggaaagca gccgtttgaa actgaaatcg accgaaacgg gccacaataa cggcatccgc 1260
aacgggctgg aagtaatacg ggccggcgag gaagtgcgcc aagcagaaca gaaactggct 1320
caagcacggt ataaattcat gctggcttat ttgcgcttgg tgaagagag cgggttaggg 1380
ttggaacagg tatttgcgga ataa 1404

```

&lt;210&gt; 88

&lt;211&gt; 467

&lt;212&gt; PRT

<213> *Neisseria meningitidis*

&lt;400&gt; 88

```

Met Thr Leu Leu Asn Leu Met Ile Met Gln Asp Tyr Gly Ile Ser Val
  1             5             10            15

```

```

Cys Leu Thr Leu Thr Pro Tyr Leu Gln His Glu Leu Phe Ser Ala Met
      20             25            30

```

```

Lys Ser Tyr Phe Ser Lys Tyr Ile Leu Pro Val Ser Leu Phe Thr Leu
      35             40            45

```

```

Pro Leu Ser Leu Ser Pro Ser Val Ser Ala Phe Thr Leu Pro Glu Ala
      50             55            60

```

```

Trp Arg Ala Ala Gln Gln His Ser Ala Asp Phe Gln Ala Ser His Tyr
      65             70            75            80

```

```

Gln Arg Asp Ala Val Arg Ala Arg Gln Gln Gln Ala Lys Ala Ala Phe
      85             90            95

```

```

Leu Pro His Val Ser Ala Asn Ala Ser Tyr Gln Arg Gln Pro Pro Ser
      100            105           110

```

```

Ile Ser Ser Thr Arg Glu Thr Gln Gly Trp Ser Val Gln Val Gly Gln
      115            120           125

```

Thr Leu Phe Asp Ala Ala Lys Phe Ala Gln Tyr Arg Gln Ser Arg Phe  
130 135 140

Asp Thr Gln Ala Ala Glu Gln Arg Phe Asp Ala Ala Arg Glu Glu Leu  
145 150 155 160

Leu Leu Lys Val Ala Glu Ser Tyr Phe Asn Val Leu Leu Ser Arg Asp  
165 170 175

Thr Val Ala Ala His Ala Ala Glu Lys Glu Ala Tyr Ala Gln Val  
180 185 190

Arg Gln Ala Gln Ala Leu Phe Asn Lys Gly Ala Ala Thr Ala Leu Asp  
195 200 205

Ile His Glu Ala Lys Ala Gly Tyr Asp Asn Ala Leu Ala Gln Glu Ile  
210 215 220

Ala Val Leu Ala Glu Lys Gln Thr Tyr Glu Asn Gln Leu Asn Asp Tyr  
225 230 235 240

Thr Asp Leu Asp Ser Lys Gln Ile Glu Ala Ile Asp Thr Ala Asn Leu  
245 250 255

Leu Ala Arg Tyr Leu Pro Lys Leu Glu Arg Tyr Ser Leu Asp Glu Trp  
260 265 270

Gln Arg Ile Ala Leu Ser Asn Asn His Glu Tyr Arg Met Gln Gln Leu  
275 280 285

Ala Leu Gln Ser Ser Gly Gln Ala Leu Arg Ala Ala Gln Asn Ser Arg  
290 295 300

Tyr Pro Thr Val Ser Ala His Val Gly Tyr Gln Asn Asn Leu Tyr Thr  
305 310 315 320

Ser Ser Ala Gln Asn Asn Asp Tyr His Tyr Arg Gly Lys Gly Met Ser  
325 330 335

Val Gly Val Gln Leu Asn Leu Pro Leu Tyr Thr Gly Gly Glu Leu Ser  
340 345 350

Gly Lys Ile His Glu Ala Glu Ala Gln Tyr Gly Ala Ala Glu Ala Gln  
355 360 365

Leu Thr Ala Thr Glu Arg His Ile Lys Leu Ala Val Arg Gln Ala Tyr  
370 375 380

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Thr Glu Ser Gly Ala Ala Arg Tyr Gln Ile Met Ala Gln Glu Arg Val  
385 390 395 400

Leu Glu Ser Ser Arg Leu Lys Leu Lys Ser Thr Glu Thr Gly Gln Gln  
405 410 415

Tyr Gly Ile Arg Asn Arg Leu Glu Val Ile Arg Ala Arg Gln Glu Val  
420 425 430

Ala Gln Ala Glu Gln Lys Leu Ala Gln Ala Arg Tyr Lys Phe Met Leu  
435 440 445

Ala Tyr Leu Arg Leu Val Lys Glu Ser Gly Leu Gly Leu Glu Thr Val  
450 455 460

Phe Ala Glu  
465

<210> 89

<211> 1404

<212> DNA

<213> *Neisseria meningitidis*

<400> 89

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ctaccggttt cactttttac ctggccacta tccctttccc catccgtttc ggcttttacg 180  
ctgctgaagc catggcgggc ggccgagcaa cattcggctg attttcaagc gtccattac 240  
cagcgtgatg cagtgcgcgc acggcaacaa caagccaagg ccgatttccct tccccatgta 300  
tccgccaatg ccagctacca gcgccagccg ccatcgattt ctcccaccgc cgaacacag 360  
ggatggagcg tgcaggtggg acaaacctta ttgacgctg ccaaatattgc acaataccgc 420  
caaagcaggt tcgatacgca ggctgcagaa cagcgtttcg atcgccgacg cgaagaattg 480  
ctgtgaaaag ttgccgaaaag ttatttcaac gttttactca gccgagacac cggtgcgcgc 540  
catgcggcgg aaaaagagggc ttatgcccag caggttaaggc aggcgcaggc ttatttcaat 600  
aaaggtgctg ccaccgcgct ggatattcac gaagccaagg ccggttacga caatgccctg 660  
accgacctgg atagcaaaaca aatcgaggcc atagataccg ccaacctgtt ggcacgctat 780  
ctgcccgaagc tggaacgtta cagtctggat gaatggcagc gcattgcctt atccaacaat 840  
catgaatacc ggatgcagca gtttgccctg caaagcagcg gacaggcgct tcgggcagca 900  
cagaacagcc gctatcccac cgtttctgcc catgtcggct atcagaataa cctctacact 960  
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cgccaggctt ataccgaaag cgggtgcggcg cgttaccaaa tcattggcga agaaccgggt 1200  
ttggaaagca gccgtttgaa actgaaatcg accgaaaccg gccacaata cggcatccgc 1260  
aaccgctgag aagtaatacg ggccggcgag gaagtgcgcc aagcagaaca gaaactggct 1320



Ile His Glu Ala Lys Ala Gly Tyr Asp Asn Ala Leu Ala Gln Glu Ile  
210 215 220

Ala Val Leu Ala Glu Lys Gln Thr Tyr Glu Asn Gln Leu Asn Asp Tyr  
225 230 235 240

Thr Asp Leu Asp Ser Lys Gln Ile Glu Ala Ile Asp Thr Ala Asn Leu  
245 250 255

Leu Ala Arg Tyr Leu Pro Lys Leu Glu Arg Tyr Ser Leu Asp Glu Trp  
260 265 270

Gln Arg Ile Ala Leu Ser Asn Asn His Glu Tyr Arg Met Gln Gln Leu  
275 280 285

Ala Leu Gln Ser Ser Gly Gln Ala Leu Arg Ala Ala Gln Asn Ser Arg  
290 295 300

Tyr Pro Thr Val Ser Ala His Val Gly Tyr Gln Asn Asn Leu Tyr Thr  
305 310 315 320

Ser Ser Ala Gln Asn Asn Asp Tyr His Tyr Arg Gly Lys Gly Met Ser  
325 330 335

Val Gly Val Gln Leu Asn Leu Pro Leu Tyr Thr Gly Gly Glu Leu Ser  
340 345 350

Gly Lys Ile His Glu Ala Glu Ala Gln Tyr Gly Ala Ala Glu Ala Gln  
355 360 365

Leu Thr Ala Thr Glu Arg His Ile Lys Leu Ala Val Arg Gln Ala Tyr  
370 375 380

Thr Glu Ser Gly Ala Ala Arg Tyr Gln Ile Met Ala Gln Glu Arg Val  
385 390 395 400

Leu Glu Ser Ser Arg Leu Lys Leu Lys Ser Thr Glu Thr Gly Gln Gln  
405 410 415

Tyr Gly Ile Arg Asn Arg Leu Glu Val Ile Arg Ala Arg Gln Glu Val  
420 425 430

Ala Gln Ala Glu Gln Lys Leu Ala Gln Ala Arg Tyr Lys Phe Met Leu  
435 440 445

Ala Tyr Leu Arg Leu Val Lys Glu Ser Gly Leu Gly Leu Glu Thr Val  
450 455 460

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Phe Ala Glu  
465

<210> 91  
<211> 29  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: primer

<400> 91  
gaacatggat ccggtccaca cactttacg 29

<210> 92  
<211> 30  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: primer

<400> 92  
gcggccgaat tccaacaggg tcaatgaagt 30

<210> 93  
<211> 34  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: primer

<400> 93  
ctgttggaat tcggcgcgtt gtagcaaaca ggct 34

<210> 94  
<211> 28  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: primer

<400> 94  
tagtacggta ccgattcact tgggtgctt 28

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<210> 95  
<211> 38  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: primer

<400> 95  
gcttctggta ccatatgagc aaacaggctg aaaccagt 38

<210> 96  
<211> 32  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: primer

<400> 96  
tcaatcctcg agttgcggct tttctgctc tt 32

<210> 97  
<211> 33  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: primer

<400> 97  
gctttgactt cattgacct gttggcattg gcc 33

<210> 98  
<211> 33  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: primer

<400> 98  
tatccaccaa ctggtcaatc gtggtcatatc cgg 33

<210> 99  
<211> 33  
<212> DNA  
<213> Artificial Sequence



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<220>

<223> Description of Artificial Sequence: primer

<400> 99

ccacgctgat tattgcttcc ttccctgttg ctg

33

<210> 100

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 100

accggcata gagtccgaac gccaatattt ttg

33

<210> 101

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 101

tgtttccac ccaaacttac

20

<210> 102

<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 102

gttcgtggat gcagacatag

20

<210> 103

<211> 33

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

&lt;400&gt; 103

gcctgacact gacgccttat ttgcaacatg aac

33

&lt;210&gt; 104

&lt;211&gt; 33

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

&lt;400&gt; 104

taccgtgctt gagccagttt ctgttctgct tgg

33

&lt;210&gt; 105

&lt;211&gt; 19

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

&lt;400&gt; 105

accgtgaggc ggacttggc

19

&lt;210&gt; 106

&lt;211&gt; 33

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

&lt;400&gt; 106

tggcccgcat tgtcgggttt aaagccgtct tcg

33

&lt;210&gt; 107

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

&lt;400&gt; 107

atttcggag ggcgaactgg

20

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<210> 108

<211> 20

&lt;212&gt; DNA

<213> Artificial Sequence

 $\langle 220 \rangle$ 

<223> Description of Artificial Sequence: primer

<400> 108

gcttcgcaaa agccgacttg

20

&lt;210&gt; 109

<211> 20

&lt;212&gt; DNA

<213> Artificial Sequence

 $\langle 220 \rangle$ 

<223> Description of Artificial Sequence: primer

<400> 109

qqcaaccqat tqccatcatc

20

 $\langle 210 \rangle$  110

<211> 20

<212> DNA

<213> Artificial Sequence

 $\langle 220 \rangle$ 

<223> Description of Artificial Sequence: primer

<400> 110

tttccgtttt cagacggctg

20

 $\langle 210 \rangle$  111

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 111

aagaccgtaa aaatgcaggc g

21

<210> 112

<211> 20

&lt;212&gt; DNA

<213> Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

&lt;400&gt; 112

tttccgaatt tgcgggagtg

20

&lt;210&gt; 113

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

&lt;400&gt; 113

ggttggtgctgc tttcaaacgc

20

&lt;210&gt; 114

&lt;211&gt; 24

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

&lt;400&gt; 114

attaaatatt ttgtccgctt gtac

24

&lt;210&gt; 115

&lt;211&gt; 33

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

&lt;400&gt; 115

aaagcacagc accatggttg cagtagccga aac

33

&lt;210&gt; 116

&lt;211&gt; 33

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Description of Artificial Sequence: primer

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PCT/EP00/06943

<400> 116

agtgtcttta gcctcaatta cagcagcact gcc

33